



REVIEW

The Role of Vessel Density as Measured by Optical Coherence Tomography Angiography in the Evaluation of Pseudoexfoliative Glaucoma: A Review of the Literature

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ABSTRACT

Introduction: To review the existing literature about the optical coherence tomography angiography (OCTA) findings regarding peripapillary and macular vessel density (VD) in patients with pseudoexfoliative glaucoma (PXG).

Methods: A comprehensive search of the PubMed database was conducted to include articles up to November 1, 2021, using an appropriate search algorithm. The retrieved articles were assessed for eligibility and filtered manually to exclude duplicates, while articles and book chapters cited in the reference lists of the eligible articles obtained by this method were reviewed so as not to miss any relevant studies.

Results: There is consistency among the studies published so far that a significant decrease in peripapillary VD exists in eyes with PXG compared to controls, and macular VD has also been reported to be significantly lower in PXG eyes than controls. However, the existing literature

remains controversial regarding OCTA findings in eyes with PXG compared to those with primary open-angle glaucoma (POAG). Several studies have found that peripapillary VD and macular VD were significantly lower in PXG than POAG, while other studies reported no significant difference.

Conclusions: Eyes with PXG were found to present decreased peripapillary and macular VD compared to control eyes, suggesting that a vascular component, including optic nerve hypoperfusion, may be implicated in the pathogenesis of PXG.

Keywords: Foveal Avascular Zone; Glaucoma; OCT Angiography; Peripapillary; Pseudoexfoliation; Vessel Density

Key Summary Points

A significant decrease in peripapillary and macular vessel density has been reported in eyes with pseudoexfoliative glaucoma in comparison with control subjects.

No general consensus exists regarding the optical coherence tomography angiography findings in patients with pseudoexfoliative glaucoma compared to patients with primary open-angle glaucoma.

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INTRODUCTION

Pseudoexfoliation syndrome (PXS) was initially described by Lindberg in 1917 and is considered a complex age-related systemic disorder of the extracellular matrix, primarily affecting the eye [1], although visceral organs, such as the lungs, liver, kidneys, gall bladder, heart and cerebral meninges, can also be involved [2–4]. In the eye, PXS is characterized by the production and progressive deposition of fibrillar material, which can be observed during slit-lamp examination as “dandruff-like” flakes in the anterior chamber, at the pupillary margin, on the lens zonules, on the trabecular meshwork and on the anterior lens capsule, forming a characteristic double concentric ring pattern [5]. It is worth noting that PXS has been associated with increased risk of glaucoma and cataract, with predisposition to intraocular complications during surgery [6].

Pseudoexfoliative glaucoma (PXG) is the most common identifiable cause of secondary open-angle glaucoma (OAG) worldwide, accounting for 25–70% of OAG and involving a high risk of blindness [7, 8]. The cumulative risk of developing glaucoma in patients with PXS has been estimated at approximately 5.3% and 15.4% at 5 and 10 years, respectively [9]. In PXG, accumulation of fibrillar extracellular material occurs, obstructing the aqueous humor outflow pathways, which in turn causes increased intraocular pressure (IOP) and subsequent glaucomatous optic nerve damage [8, 10]. PXG is often characterized by higher IOP and greater IOP fluctuation, resulting in faster progression compared to primary OAG (POAG) [6, 11, 12]. However, PXG with controlled IOP has also been reported to progress more rapidly than POAG, suggesting that an IOP-independent pathogenic mechanism exists in PXG [13]. Specifically, the thickness and stiffness of the lamina cribrosa was thinner and lower in PXG patients compared with those in POAG patients [14, 15]. Moreover, previous studies have suggested that a vascular mechanism, including decreased ocular blood flow and consequent reduced optic nerve perfusion due to changes in the blood vessel walls and endothelial

dysfunction, may be implicated in the pathogenesis of PXG [16, 17].

Various methods have been used to measure optic nerve head perfusion in both POAG and PXS [18]. Fluorescein angiography has been applied to measure vascular blood flow; however, it is both invasive and inaccurate for the measurement of optic nerve head perfusion, while laser speckle flowmetry and Doppler imaging are operator-dependent and do not provide adequate visualization [19, 20]. Optical coherence tomography angiography (OCTA) is a relatively new noninvasive imaging technology, allowing visualization of the retinal microcirculation, also providing quantitative analysis of the peripapillary and macular microvasculature [21, 22]. Since it has been hypothesized that impaired vascular supply may also be involved in the pathogenesis of PXG, several studies have used OCTA to investigate peripapillary and macular microcirculation in eyes with PXG and PXS [20, 23–37]. Based on the above, the purpose of this review is to assess the peripapillary and macular vessel density (VD) as measured using OCTA in eyes with PXG, as well as to compare these OCTA parameters in eyes with PXG with those of either eyes with POAG or normal eyes, based on findings reported in the existing literature.

METHODS

A comprehensive search of the PubMed database was conducted to include articles up to November 1, 2021, using the following search algorithm: [(“pseudoexfoliative” OR “pseudoexfoliation” OR “exfoliation” OR “exfoliative”) AND (“glaucoma”) AND (“optical coherence tomography angiography” OR “OCT angiography” OR “OCTA” OR “vessel density” OR “blood flow” OR “vascularity”)]. The retrieved articles were assessed for eligibility and filtered manually to exclude duplicates, while articles and book chapters cited in the reference lists of the eligible articles obtained by this method were reviewed, so as not to miss any relevant study. No language restrictions were set. This article is based on previously conducted studies and does not contain any new

Table 1 Characteristics and main findings of the studies included in the review

Study	Region	Study Design	N Eyes	Imaging Model-Protocol	Key Messages	Limitations
Suwan [23]	New York	Cross-sectional	33 PXS 43 PXG 31 POAG 45 controls	AngioVue Avanti RTVue XR, OptoVue— 4.5 × 4.5	Both POAG and PXG demonstrated decreased perfused capillary density compared to controls PXG demonstrated significantly lower perfused capillary density values compared to POAG, after adjusting for age and stage	Small sample size High proportion of older-age patients in the PXS and PXG groups (age and stage-adjustment)
Park [24]	Korea	Cross-sectional, retrospective	39 PXG 39 POAG	DRI OCT Triton; Topcon, Tokyo, Japan	Average peripapillary VD was significantly lower in PXG than in POAG with similar severity	Small sample size Retrospective design Lack of control group Probably included normal-tension glaucoma eyes
Rebolleda [25]	Spain	Cross-sectional	20 PXG 20 POAG 20 controls	AngioVue Avanti RTVue XR, OptoVue— 4.5 × 4.5 AngioPlex, Zeiss	Peripapillary capillary VD was significantly lower in PXG than in POAG Both machines showed that peripapillary capillary VD was lower in PXG and POAG than controls	Small sample size

Table 1 continued

Study	Region	Study Design	N Eyes	Imaging Model-Protocol	Key Messages	Limitations
Philip [26]	New York	Cross-sectional	26 PXG 28 POAG	AngioVue Avanti RTVue XR, OptoVue— 3 × 3 macula	PXG presented statistically significantly lower macular VD in the SCP in all areas compared to POAG, even after correction for age, stage, axial length, race	Small sample size High proportion of older age patients in the PXG group
Pradhan [27]	India	Cross-sectional, prospective	39 PXG 39 POAG	AngioVue Avanti RTVue XR, OptoVue— 4.5 × 4.5 ONH and 3 × 3 macula	There was no significant difference in peripapillary and parafoveal superficial VD between PXG and POAG The choroidal microvasculature drop-out was significantly lower in PXG than in POAG	Projection artifacts in OCTA Older age of PXG compared to POAG Selection bias, including patients visiting eye clinic Effect of blood pressure, systemic antihypertensive medications and ocular hypotensive drops was not assessed
Çınar [28]	Turkey	Cross-sectional	35 PXS 35 controls	AngioVue Avanti RTVue XR, OptoVue— 6 × 6 macula	Significant difference in superficial VD between PXS and controls FAZ area was significantly enlarged in PXS in both SCP and DCP compared to controls	Small sample size

Table 1 continued

Study	Region	Study Design	N Eyes	Imaging Model-Protocol	Key Messages	Limitations
Lommatzsch [29]	Germany	Cross-sectional, prospective	21 PXG 40 POAG	AngioVue Avanti RTVue XR, OptoVue— 4.5 × 4.5 ONH and 6 × 6 macula	No significant differences in the papillary, peripapillary and macular VD between PXG and POAG	Small sample size Patients receiving local anti-glaucomatous agents Exclusion of patients with arterial hypertension or hypotension
Jo [30]	Korea	Cross-sectional, retrospective	49 PXG 49 POAG	AngioVue Avanti RTVue XR, OptoVue— 4.5 × 4.5 ONH and 6 × 6 macula	No significant difference in peripapillary VD between PXG and POAG Parafoveal VD in both superficial and deep plexus was significantly lower in PXG than POAG Perifoveal VD only in deep plexus was significantly lower in PXG than POAG	Retrospective design Selection bias, including only patients visiting eye clinic
Simsek [31]	Turkey	Cross-sectional, prospective	40 PXG 40 controls	AngioVue Avanti RTVue XR, OptoVue— 4.5 × 4.5 ONH	Significant decrease in optic nerve head VD in all regions in PXG compared to controls	Small sample size
Tangrammaruk [20]	Thailand	Cross-sectional	31 PXS 32 controls	AngioVue Avanti RTVue XR, OptoVue— 4.5 × 4.5 ONH	Significantly lower peripapillary capillary VD in PXS than in control	Small sample size Any stage of PXS

Table 1 continued

Study	Region	Study Design	N Eyes	Imaging Model-Protocol	Key Messages	Limitations
Köse [32]	Turkey	Cross-sectional, retrospective	46 PXG 36 POAG 23 controls	AngioVue Avanti RTVue XR, OptoVue— 4.5 × 4.5 ONH and 6 × 6 macula	VD was significantly lower in PXG and POAG eyes than in controls in all peripapillary sectors The average macular SCP VD was significantly lower in PXG than in POAG	Small sample size Older patients with PXG and POAG (adjustment for age) Patients on antiglaucoma drops
Subasi [33]	Turkey	Cross-sectional, prospective	34 PXG 36 POAG	AngioVue Avanti RTVue XR, OptoVue— 4.5 × 4.5 ONH and 6 × 6 macula	In PXG, all VD parameters in the macular region were significantly lower than in POAG FAZ area was larger in PXG than POAG, but difference did not reach significance Peripapillary VD was significantly lower in PXG than in POAG	Small sample size Lack of controls
Safizadeh [34]	Iran	Cross-sectional, prospective	41 PXS 82 PXG 57 controls	AngioVue Avanti RTVue XR, OptoVue— 4.5 × 4.5 ONH	PXG presented lower peripapillary VD than controls and PXS	Small sample size Confounding factors that could influence VD, including systemic hypertension, diabetes mellitus and vasoactive medications (both topical and systemic) were not excluded Older patients in PXG and POAG (adjusting for age and gender)

Table 1 continued

Study	Region	Study Design	N Eyes	Imaging Model-Protocol	Key Messages	Limitations
Onur [35]	Turkey	Cross-sectional	18 PXG 18 POAG 18 controls	AngioVue Avanti RTVue XR, OptoVue— 3 × 3	Peripapillary capillary VD was significantly lower in POAG and PXG compared to controls Peripapillary capillary VD did not differ between POAG and PXG	Small sample size Use of 3 × 3 imaging modality
Durmuş Ece [36]	Turkey	Cross-sectional, prospective	25 PXG 25 POAG 25 controls	AngioVue Avanti RTVue XR, OptoVue— 4.5 × 4.5 ONH and 6 × 6 macula	In glaucomatous eyes, VD values were significantly lower than controls No difference in VD between POAG and PXG	Small sample size Lack of blood pressure parameters
Gür Güngör [37]	Turkey	Cross-sectional	39 PXS 39 controls	AngioVue Avanti RTVue XR, OptoVue— 4.5 × 4.5 ONH and 6 × 6 macula	No statistically significant difference in peripapillary VD between PXS and controls In the macular region, superficial VD parameters were significantly lower in PXS than controls	Small sample size

Table 1 continued

Study	Region	Study Design	N Eyes	Imaging Model-Protocol	Key Messages	Limitations
Cornelius [38]	Germany	Cross-sectional, prospective	26 POAG 23 PXG	Cirrus HD-OCT with AngioPlex Metrix	The mean superficial perifoveal plexus perfusion density was significantly lower in PXG eyes than in POAG eyes The mean perfusion density for superficial peripapillary plexus did not differ between POAG and PXG eyes	Small sample size

PXS pseudoexfoliation syndrome; *PXG* pseudoexfoliation glaucoma; *POAG* primary open-angle glaucoma; *SCP* superficial capillary plexus; *DCP* deep capillary plexus; *VD* vessel density; *FAZ* foveal avascular zone; *ONH* optic nerve head

studies with human participants or animals performed by any of the authors.

RESULTS

Table 1 summarizes the characteristics and the main findings of the studies included in this review. All studies were cross-sectional, either prospective or retrospective. In all studies except two, the AngioVue Avanti RTVue XR (Optovue, Fremont, CA) OCTA imaging model was used to measure the vessel density (VD) in various regions and foveal avascular zone (FAZ) area.

Pseudoexfoliation Syndrome vs. Controls

Three cross-sectional studies compared eyes with PXS with age-matched control eyes [20, 28, 37]. Regarding VD in the macular area, there was consistency in that a significant decrease in superficial VD was observed in eyes with PXS compared to controls [28, 37], accompanied by a significant enlargement in

the FAZ area in both the superficial capillary plexus (SCP) and deep capillary plexus (DCP) in eyes with PXS compared to control eyes [28]. However, the findings related to peripapillary VD seemed to be contradictory, with Tangtammaruk et al. reporting a significant decrease in peripapillary perfused capillary density in eyes with PXS versus controls [20], in line with Suwan et al. [23], while Gür Güngör et al. found no significant difference in peripapillary VD between the two groups [37].

Pseudoexfoliation Glaucoma vs. Controls

Simsek et al., in a prospective, cross-sectional study, compared 40 eyes with PXG and 40 age-matched control eyes and demonstrated that there was a significant decrease in peripapillary VD in all regions in eyes with PXG compared to controls [31], in agreement with other studies [23, 34–36], as well as with Köse et al., who found that both peripapillary and macular VD were lower in PXG eyes than in controls [32]. In addition, the abovementioned findings were in

line with Rebolleda et al., who reached the same conclusion using two different OCTA machines [25].

Pseudoexfoliation Glaucoma vs. Primary Open-Angle Glaucoma

The existing literature remains controversial regarding the OCTA findings in eyes with PXG compared to POAG. Several studies have found that average peripapillary VD was significantly lower in eyes with PXG than in POAG eyes [24, 25, 33], while peripapillary VD was found to be affected mainly in the inferonasal and nasal sectors [24, 26, 32]. Interestingly, a significant correlation between peripapillary VD and retinal nerve fiber layer (RNFL) thickness, as well as visual field defects, was also reported [24]. Moreover, macular VD was found to be lower in PXG compared to POAG [26, 32, 33], especially in the parafoveal area and perifoveal DCP [30]. Additionally, the FAZ area was reported to be increased in eyes with PXG compared to POAG, although it did not reach significance [33]. It is worth noting that these observations were independent of glaucoma severity, since they were observed with similar severity in PXG and POAG [24].

On the other hand, there are also studies which did not note any significant difference in peripapillary VD [27, 29, 30, 35, 36, 38] or in foveal and parafoveal VD [27, 29, 36] between eyes with PXG and POAG.

DISCUSSION

Our results clearly showed that eyes with PXG presented significantly decreased peripapillary and macular VD compared to controls. On the other hand, there is controversy regarding the OCTA findings in eyes with PXG compared to those with POAG, since most of the studies demonstrated that peripapillary and macular VD was lower in eyes with PXG than with POAG, but some authors reported finding no difference in OCTA parameters between PXG and POAG.

The discrepancy in the OCTA outcomes between eyes with PXG and POAG may be

attributed to the different study design, methodologies and devices used in the studies published so far. Specifically, although most studies used the AngioVue Avanti RTVue XR OCTA system, there was no consistency among studies in the parameters examined, since several indices including global, annular or average VD were used; therefore, a quantitative analysis of the results, comparing eyes with PXG, POAG and controls, was not feasible. It should also be taken into account that in some studies the authors did not match the subjects' age or glaucoma severity between groups, and they used custom software to measure and compare VD, which may have affected their results [23, 24]. The decreased VD in eyes with PXG compared to eyes with POAG corroborates the present understanding of PXG as a particularly aggressive type of glaucoma, which often progresses at a more rapid rate and responds more poorly to medical treatment compared to POAG. Similarly, prior studies reported increased vascular resistance in the ophthalmic artery in PXG [39].

The main mechanism of glaucomatous optic neuropathy in eyes with PXG has been considered to be mechanical damage due to elevated IOP, which causes the death of retinal ganglion cells [40]. However, it has been demonstrated that vascular abnormalities may be another important causative factor [10]. Specifically, pseudoexfoliative material has been shown to accumulate mainly in smaller vessel endothelial cells, smooth muscle cells and pericytes, which have a regulatory role in local microcirculation, further leading to extirpation of the vessel wall or obliteration of the lumen [41]. As a result, pseudoexfoliative deposits in vessels may cause circulation deficiency or occlusion, inducing ischemic changes. This hypothesis is supported by the fact that decreased peripapillary and macular VD has been observed in eyes with PXG.

It is worth mentioning that peripapillary VD has been found to be affected mainly in the inferonasal and nasal sectors [24, 32]. This can be explained by the fact that the nasal part of the lamina cribrosa in PXG eyes may be more vulnerable to glaucomatous damage. Yüksel et al. used color Doppler imaging to evaluate

the orbital blood flow velocities and found that the peak systolic velocity and end-diastolic velocity of the posterior nasal ciliary artery were significantly decreased in PXG eyes compared to eyes with PXS [16]. The impaired retrobulbar blood flow in the nasal part of the lamina cribrosa might have induced weakness in the corresponding lamina cribrosa, rendering the nasal part more susceptible to glaucomatous damage.

An interesting point that should be noted is that in the macular area, the SCP was found to be mainly affected in eyes with PXG compared to POAG, although Jo et al. reported that VD was also significantly decreased in the parafoveal area and perifoveal DCP in eyes with PXG [30]. It is already known that the SCP is responsible for the metabolic supply of the ganglion cell layer, whereas the DCP is important for the nutrition of the inner nuclear layer, which comprises bipolar cells, horizontal cells and amacrine cells [42, 43]. Eltutar et al. demonstrated that the ganglion cell layer and superficial retinal layer were significantly thinner in eyes with PXS and that this thinning may be an early sign of PXG [42]. The reduced VD in the superficial retinal layers may explain the thinning of the ganglion cell layer, which has been described previously [42], or it could be secondary to a reduction in RNFL and ganglion cell layer. Longitudinal studies are required to understand the pathogenesis of reduced VD in patients with PXG.

Potential limitations of the review pertain to the inherent limitations of each separate study. Firstly, the sample size in some studies was small. Secondly, the cross-sectional and mainly retrospective design is a significant limitation of the included studies, while some of them lacked a control group. Additionally, there was high heterogeneity between the included studies, providing different OCTA parameters and values, and therefore precluding a quantitative analysis of the comparison between eyes with POAG, PXG and controls. Finally, measurement of the VD and FAZ area was performed using custom software, and artifacts should also be taken into account when analyzing the results of each study.

CONCLUSIONS

In conclusion, the current review clearly showed that eyes with PXG were found to present decreased peripapillary and macular VD compared to control eyes, suggesting that there is a vascular component, including optic nerve hypoperfusion, in the pathogenesis of PXG. Furthermore, the RNFL and ganglion cell loss should be considered to explain the decreased VD. On the other hand, controversy exists regarding the OCTA findings in eyes with PXG compared to POAG. Further comparative studies with large sample size are needed to scrutinize our results.

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Author Contributions. Irimi Chatziralli performed the literature review, analyzed and interpreted data, as well as drafted the manuscript; Ilias Milionis, Aikaterini Christodoulou and Panagiotis Theodossiadis interpreted data and critically revised the manuscript; George Kitsos conceived the topic of the review, analyzed data and critically revised the manuscript.

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Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with

human participants or animals performed by any of the authors.

Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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