Acta Ophthalmologica



Review Article

# Vascular biomarkers from optical coherence tomography angiography and glaucoma: where do we stand in 2021?

Joshua D. Shin,[1,†] Amber T. Wolf,[2,†] Alon Harris,[2] Alice Verticchio Vercellin,[2] Brent Siesky,[2] Lucas W. Rowe,[3] Michelle Packles[2] and Francesco Oddone[4]

[1]School of Medicine, New York Medical College, Valhalla, NY, USA
[2]Icahn School of Medicine at Mount Sinai Hospital, New York, NY, USA
[3]Indiana University School of Medicine, Indianapolis, IN, USA
[4]IRCCS –Fondazione Bietti, Rome, Italy

**ABSTRACT.**
**Biomarkers of ocular blood flow originating from a wide variety of imaging modalities have been associated with glaucoma onset and progression for many decades. Advancements in imaging platforms including optical coherence tomography angiography (OCTA) have provided the ability to quantify vascular changes in glaucoma patients, alongside traditional measures such as retinal nerve fibre layer thickness and optic nerve head structure. Current literature on vascular biomarkers, as measured by OCTA, indicates significant relationships between glaucoma and blood flow and capillary density in the retina and ONH. The data currently available, however, are highly diverse and lack robust longitudinal data on OCTA vascular outcomes and glaucoma progression. Herein we discuss and summarize the relevant current literature on OCTA vascular biomarkers and glaucoma reviewed through March 1, 2021. Associations between OCTA vascular biomarkers and clinical structural and functional glaucoma outcomes as well as differences between glaucoma patients and healthy controls are reviewed and summarized. The available data identify significantly decreased flow density, flow index and vessel density in the ONH, peripapillary vascular layer and macula of glaucoma patients compared with controls. Whole image vessel density is also significantly decreased in glaucoma patients compared with controls, and this outcome has been found to correspond to severity of visual field loss. OCTA vascular biomarkers alongside clinical structural outcomes may aid in assessing overall risk for glaucoma in patients.**

**Key words:** OCTA – glaucoma – vascular biomarkers – imaging

All authors made substantial contribution to the review. Each author participated in drafting or revising the manuscript and approved the submitted version for publication.

Acta Ophthalmol. 2022: 100: e377–e385


doi: 10.1111/aos.14982

## Introduction

Open-angle glaucoma (OAG) is a leading cause of irreversible blindness, affecting over 70 million people worldwide (Weinreb et al., 2014). Although our understanding of the disease has significantly evolved, it was traditionally characterized as optic neuropathy with retinal ganglion cell death related to a high intraocular pressure (IOP) (Weinreb et al., 2014). However, despite reduction of IOP or it being within normal limits, many patients experience disease onset and continued progression. In certain patients, vascular changes in the retina and optic nerve head have been linked with glaucoma onset and progression of the disease (Weinreb & Harris, 2009). Despite its relevance, a lack of gold standard in ocular vascular imaging and historically invasive, highly technical and fragmented approach have prevented the widespread adoption of vascular biomarkers in glaucoma management.

Due to OCTA's ability to accurately detect clinical structural changes alongside ocular blood flow biomarkers, it offers a novel approach to aid in diagnosis and management of glaucoma. Within the current literature, studies have investigated using OCTA to detect various types of glaucoma, including exfoliation glaucoma, normal-tension glaucoma, angle-closure glaucoma and OAG (Lommatzsch et al., 2019; Hou et al. 2020). This review summarizes the relevant literature on the use of OCTA vascular biomarkers in glaucoma and discusses their specific meaning and use in determining overall risk for glaucoma onset and progression.

## Material and methods

Optical coherence tomography angiography (OCTA) is an imaging platform that is noninvasive with a dye-less

modality to detect endoluminal blood flow changes within the retina and optic nerve head (ONH) (Kromer et al., 2019). Previously used imaging modalities to evaluate blood flow in the retina include highly invasive fluorescein angiography (FA) and indocyanine green angiography (ICGA) (de Carlo et al., 2015). Although FA remains valuable in identifying choroidal and vascular neovascularization and leaks, it is not an ideal modality for localizing decreased blood flow to a specific layer of the eye and can even obscure certain pathologies (de Carlo et al., 2015). Other limitations include the invasive nature of the procedure (dye is injected systemically into a vein), cost and time spent performing the procedure (de Carlo et al., 2015). There is also a small risk of anaphylaxis, as well as specific contraindications for ICGA (de Carlo et al., 2015). Advantages of OCTA include its non-invasive nature, the collection of both structural and vascular data simultaneously and its ability to analyse the images in cross-section to better localize the pathology (de Carlo et al., 2015; Spaide et al., 2018). Classic Doppler OCT had major limitations in directly measuring blood flow as blood flow is the perpendicular direction of the OCT beams (Spaide et al., 2018). Blood velocity can be determined but only through complex calculations, including the knowledge of the Doppler angle, the angle between the light beam and blood vessel (Spaide et al., 2018). Comparatively, OCTA can capture the microvascular structure like a classic OCT device while also localizing the depth of the lesion and affected capillary layer, making it unique with this dual functionality (Spaide et al., 2018).

Specifically, OCTA compares sequential B-scans acquired at a single location within the eye (Wan & Leung, 2017). As static structures would not be expected to change, changes between sequential images are indicative of blood flow in the region of interest (Wan & Leung, 2017). The main vascular outcomes that can be measured include vessel density (% of detected vessel area/total imaged area), flow index (average decorrelation signal reported as a number between 0 and 1) and blood flux index (mean flow intensity in vessel area divided by full dynamic range of blood flow signal intensity normalized to a number between 0 and 1) (Wan & Leung, 2017). There are additional algorithms such as split-spectrum decorrelation angiography (SSADA) and optical microangiography (OMAG) based on OCTA B-scan images to approximate blood flow parameters (Wan & Leung, 2017). In 2017, available OCTA devices include models from Optovue, Spectralis, Heidelberg and Zeiss (Munk et al., 2017). In a head-to-head comparison, researchers found no significant differences in vessel density measurements but found differences in the number of vessel bifurcations to be statistically significant ($p \leq 0.001$) (Munk et al., 2017).

A comprehensive literature search was conducted from December 14, 2020 through March 1, 2021 on PubMed, Medline, Google Scholar and associated digital platforms with the following keywords: OCTA, Angio-OCT, vascular, blood flow, vascular imaging, retina, glaucoma, haemodynamics, biomarkers, vessel density, ocular perfusion pressure, perfusion, vascular and vessels. The associated articles were also searched and cross-referenced for relevant citations. There were no publication year restrictions. Review articles and non-English articles were excluded, as well as studies using OCTA only to capture structural measurements and not vascular biomarkers of the eye. The age of subjects for included publications did not significantly differ. After applying the inclusion and exclusion criteria, 28 studies were eligible for this review. Studies are grouped into categories by locality of vascular measure, specifically peripapillary and circumpapillary and optic nerve head (ONH), macula and fovea, and choroid.

# Results

### Optic nerve head and peripapillary and circumpapillary capillary layer OCTA vascular biomarkers

Optical coherence tomography angiography (OCTA) vascular biomarkers of the optic nerve head and peripapillary and circumpapillary capillary layers are found in Table 1. Specifically, Jia et al. (2012) found that in pre-perimetric glaucomatous (PPG) eyes, the whole disc flow index significantly reduced (35%) compared with healthy controls.[9] The flow index also greatly reduced in the temporal ellipse of the disc (57%) in PPG eyes compared with controls (Jia et al., 2012). Jia and colleagues also found a significant decrease in vessel density in both the whole disc area and temporal ellipse of the disc by 34% and 57%, respectively (Jia et al., 2012). Jia et al. (2014) using OCTA and an SSADA further demonstrated a decreased blood flow index in glaucomatous eyes in the area of the optic disc (Jia et al., 2014). Vessel density loss in glaucomatous eyes was also demonstrated in the optic nerve head by Lévêque et al. (2016), showing a decrease in both the total and the temporal vessel density 24.7% and 22.88% respectively (Lévêque et al., 2016).

Glaucomatous vascular changes were also found in the peripapillary capillary layer. Liu et al. (2015) showed a significant decrease in both the flow density and vessel density of the peripapillary layer in glaucomatous eyes compared with healthy controls. Using OMAG, Chen et al. (2016) found a lower blood flux index in the peripapillary layer in glaucomatous eyes than healthy controls (Chen et al., 2016). Chen et al. (2017) also found decreased vessel density in both the macular and peripapillary areas as well as in the whole image in glaucomatous eyes (Chen et al., 2017). Furthermore, circumpapillary vessel density significantly decreased in glaucomatous eyes (Chen et al., 2017). Chen et al. (2020) demonstrated that eyes with POAG had more areas of low perfusion in the peripapillary layer than controls and greater areas of focal perfusion loss (Chen et al., 2020). Notably, Mammo et al. (2016) found that vessel density significantly decreased in the radial peripapillary layer in the glaucomatous eye of patients with unilateral glaucoma compared with the unaffected eye, glaucoma suspects and healthy controls (Mammo et al., 2016). Similar results by Kim et al. (2017) showed patients with unilateral perimetric glaucoma had significantly greater vessel density loss in the peripapillary and inferotemporal capillary beds than the fellow eye with pre-perimetric glaucoma (Kim et al., 2017).

These results show that even within a single patient, OCTA vascular progression can be different for each eye. Triolo et al. (2017) compared 40 normal subjects, 40 glaucoma suspects and 40 glaucoma patients and found that peripapillary vessel perfusion density

**Table 1.** Peripapillary/circumpapillary/optic nerve head (ONH) optical coherence tomography angiography (OCTA) vascular biomarkers.

| Author (year) | Patients | OCTA scan | Results | p-value |
|---|---|---|---|---|
| Jia et al. (2012) | 4 pre-perimetric glaucoma (PPG) patients<br>4 healthy subjects | Whole-disc | Whole-disc flow index was reduced by 35% in the PPG group | p = 0.040 |
| | | | Whole-disc vessel area was reduced by 34% in the PPG group | p = 0.045 |
| | | Regional disc perfusion based on the temporal ellipse of disc | Temporal ellipse of the disc flow index was reduced by 57% in the PPG group | p = 0.010 |
| | | | Temporal ellipse of disc vessel density was reduced by 57% in the PPG group | p = 0.013 |
| Jia et al. (2014) | 11 glaucoma patients<br>24 healthy subjects | 3 × 3 mm, using SSADA algorithm | Disc flow index was reduced by 25% in the glaucoma group | p = 0.003 |
| Lévêque et al. (2016) | 50 glaucoma patients<br>30 normal subjects | 3 × 3 mm ONH | Total ONH vessel density was reduced by 24.7% in glaucoma group compared with control group | p < 0.0001 |
| | | | Temporal disc vessel density was significantly reduced by 22.88% in the glaucoma group compared with the control group | p = 0.001 |
| Liu et al. (2015) | 12 OAG<br>12 healthy subjects | 3 × 3-mm ONH | Peripapillary flow density was significantly lower in glaucomatous eyes than that in controls | p < 0.001 |
| | | | Peripapillary vessel density was significantly lower in glaucomatous eyes than that in normal controls | p < 0.001 |
| Chen et al. (2016) | 42 OAG subjects<br>26 glaucoma suspect subjects<br>20 normal subjects | OMAG, OCT-A<br>2.4 × 2.4 mm | Eyes from OAG subjects and glaucoma suspects showed significantly lower blood flux index than normal eyes | p ≤ 0.0015 |
| Chen et al. (2020) | 47 OAG<br>36 normal participants | ONH 4.5 × 4.5 mm | OAG patients had significantly more areas of low perfusion in the peripapillary retina than normal controls | p < 0.001 |
| | | | Focal perfusion loss was greater in OAG patients than normal controls | p < 0.001 |
| Chen et al. (2017) | 26 OAG<br>27 healthy subjects | 4.5 × 4.5 mm ONH<br>6.0 × 6.0 mm Macula | In OAG, whole-image vessel density was significantly lower than that in healthy controls in the macular and peripapillary areas | p < 0.001 |
| | | | Circumpapillary vessel density was significantly decreased compared with controls | p < 0.001 |
| Mammo et al. (2016) | 5 subjects with unilateral glaucoma<br>3 glaucoma suspect patients<br>9 normal subjects | 2 × 2 mm ONH | Vessel density in the radial peripapillary capillary network was significantly lower in glaucomatous eyes than that in matched regions in the nonaffected eye, glaucoma suspect and normal groups | P < 0.001 for all groups |
| Kim et al. (2017) | 13 patients (unilateral perimetric normal tension glaucoma, fellow eye pre-perimetric normal tension glaucoma)<br>9 healthy controls | 4.5 × 4.5 mm ONH | Vessel density in the whole peripapillary region in the eyes with perimetric glaucoma were significantly lower than that in pre-perimetric glaucomatous eyes | p = 0.001 |
| | | | Vessel density in the inferotemporal region in perimetric glaucoma eyes were significantly lower than that in pre-perimetric glaucomatous eyes | p < 0.001 |
| Triolo et al. (2017) | 40 normal controls<br>40 glaucoma suspect<br>40 glaucoma | 6 × 6-mm fovea, ONH | Average peripapillary vessel perfusion density was significantly decreased in the glaucoma group | p ≤ 0.001 |
| | | | Peripapillary vessel perfusion density was decreased in the superior and inferior quadrants in the glaucoma group | p ≤ 0.001 |
| Mansoori et al. (2017) | 24 OAG<br>52 normal subjects | 3.45 × 3.45 mm ONH using Bar-Selective Combination of Shifted Filter Responses (B-COSFIRE) | Radial peripapillary capillary density was decreased in the inferotemporal sector compared with normal controls | p = 0.002 |
| | | | Radial peripapillary capillary density was decreased in the superotemporal sector compared with normal controls | p = 0.008 |
| Akil et al. (2017) | 20 mild OAG | | | p = 0.0002 |

**Table 1** (Continued)

| Author (year) | Patients | OCTA scan | Results | p-value |
|---|---|---|---|---|
| | 20 pre-perimetric glaucoma<br>16 controls | 3 × 3 mm ONH using 1050 nm wavelength swept source OCT | Optic nerve head vessel density was significantly decreased in pre-perimetric glaucoma patients compared with controls | |
| | | | Peripapillary density was significantly decreased in pre-perimetric glaucoma patients compared with controls | p = 0.007 |
| | | | Optic nerve head vessel density was significantly decreased in OAG glaucoma compared with pre-perimetric glaucoma patients | p = 0.002 |
| | | | Peripapillary vessel density was significantly decreased in OAG patients compared with pre-perimetric glaucoma patients | p = 0.001 |
| Lu et al. (2020) | 41 normal<br>44 pre-perimetric OAG (PPG)<br>42 early perimetric OAG (EG) | ONH 4.5 mm × 4.5 mm<br>Radial peripapillary density measured using 750 μm wide elliptical annulus around disc | Inferior-temporal radial peripapillary capillary vessel density was lower in the EG group than that in controls | p < 0.05 |
| Yarmohammadi et al. (2016a) | 23 healthy subjects<br>37 glaucoma suspect<br>104 OAG | 4.5 × 4.5-mm ONH | Circumpapillary vessel density was significantly lower in the OAG group than that in glaucoma suspects compared with healthy controls (55.1 versus 60.3% versus 64.2) | p < 0.001 |
| | | | Whole-image capillary density was significantly lower in the OAG group than that in glaucoma suspect compared with healthy controls (46.2% versus 51.3% versus 56.6%) | p < 0.001 |
| Yarmohammadi et al. (2016b) | 31 healthy subjects<br>48 glaucoma suspect<br>74 glaucoma patients | 4.5 × 4.5 mm ONH | Whole image vessel density was highest in healthy subjects followed by glaucoma suspects, then mild glaucoma, lastly moderate to severe glaucoma (55.5% versus 51.3% versus 48.3% versus 41.7%) | p < 0.001 |
| | | 750-μm-wide elliptical annulus around the optic disc | Circumpapillary vessel density was highest in healthy controls and lowest in severe glaucomatous eyes (62.8% versus 49.6%) | p < 0.001 |
| Yarmohammadi et al. (2018) | 33 healthy subjects<br>33 OAG with a VF defect in one eye and normal VF in other eye | 4.5 × 4.5 mm RNFL<br>3 × 3 mm fovea | In OAG patients, whole-image vessel density in the perimetrically unaffected eye (52.0%) was greater than that in the perimetrically affected eye (48.8%) | p < 0.001 |
| | | | Whole-image vessel density was greatest in normal subjects (55.9%) | |
| Jesus et al. (2019) | 40 healthy subjects<br>82 glaucoma patients | 3 × 3 mm optic disc-centred | Significantly lower circumpapillary microvascular density in the glaucoma group than the healthy group | p < 0.001 |

decreased in the superior and inferior quadrants in glaucoma patients (Triolo et al., 2017). The average peripapillary vessel perfusion density was also decreased (Triolo et al., 2017). Similar findings by Mansoori et al. (2017) showed a significant decrease in the radial peripapillary capillary density in the inferotemporal and superotemporal regions compared with normal healthy controls (Mansoori et al., 2017). Akil et al. (2017) also demonstrated a significantly greater vessel density loss in the optic nerve head and peripapillary region in OAG patients than pre-perimetric glaucoma patients, as well as a significant decrease between pre-perimetric glaucoma and healthy controls (Akil et al., 2017). Lu et al. (2020) also demonstrated a significant decrease in vessel density of the inferior temporal radial peripapillary capillary layer in early perimetric OAG patients compared with controls (Lu et al., 2020).

Four articles were included in the review that examined circumpapillary vessel density and whole image capillary density (Yarmohammadi et al., 2016a; Yarmohammadi et al., 2016b; Yarmohammadi et al., 2018; Jesus et al., 2019). Yarmohammadi et al., (2016a) found that circumpapillary vessel density and whole image capillary density were significantly lower in eyes with OAG than those in glaucoma suspects and healthy controls. These measurements had similar diagnostic accuracy as retinal nerve fibre layer thickness in differentiating between glaucoma and healthy eyes. Another study by Yarmohammadi and colleagues (2016b) studied the associations between severity of visual field loss and vessel density, specifically circumpapillary and whole image, measured by OCTA in subjects with OAG. Their findings showed that eyes with severe glaucoma had the lowest circumpapillary vessel density, whereas healthy controls had the highest (49.6% versus 62.8%, $p < 0.001$) (Yarmohammadi et al., 2016b). Similarly, Jesus et al.

(2019) found significantly lower circumpapillary microvasculature density (cpmVC) among glaucoma patients than healthy controls ($p < 0.001$), as well as a reduction in cpmVD variation in glaucoma patients (Jesus et al., 2019). Yarmohammadi et al., 2016b also found that whole-image vessel density decreased as the severity of glaucoma increased (healthy, then glaucoma suspect, then mild glaucoma and lastly moderate to severe glaucoma). These findings are consistent with a study conducted by Yarmohammadi et al. (2018), which studied OAG patients with a visual field defect in one eye and normal visual field in the other eye, compared with healthy controls (Yarmohammadi et al., 2018). They found that whole-image vessel density in the unaffected eye (52.0%) was greater than that in the affected eye (48.8%) in OAG patients and that whole-image vessel density was greatest in normal subjects (55.9%) (Yarmohammadi et al., 2018). These results demonstrate a significantly decreased vessel density in glaucomatous eyes in the area of the optic nerve head, and peripapillary and circumpapillary vascular layers as measured by OCTA.

#### Macula, fovea and perifoveal OCT-A vascular biomarkers

Although glaucoma is mostly known to cause peripheral vision loss, damage can occur to retinal ganglion cells residing in the macula. Therefore, studying the macula and fovea can provide crucial evidence for the detection of glaucoma (Takusagawa et al., 2017). Relevant studies measuring macula, fovea and perifoveal vascular biomarkers for glaucoma are listed in Table 2. Takusagawa et al. (2017) used OCTA to detect macular perfusion defects in 30 subjects with perimetric glaucoma and 30 age-matched normal participants. They found that the superficial vascular complex (SVC) and all-plexus retinal vessel density were lower in the glaucoma group than those in the normal group ($p < 0.001$ for both) and that among all macular vessel density parameters studied, the SVC vessel density showed the best diagnostic accuracy (Takusagawa et al., 2017). However, Takusagawa et al. (2017) did not find a significant difference in vessel density within the intermediate or deep capillary plexuses. Choi et al. (2017) also studied macular vessel density and the foveal avascular zone (FAZ) in 52 patients with OAG and 52 healthy controls (Choi et al., 2017).

Unlike Takusagawa et al. (2017), Choi and colleagues found that macular vessel density was significantly lower in OAG patients in the superficial layer, deep layer and whole retina. (Choi et al., 2017). This finding is consistent with Kromer et al. (2019), who found that macular flow density was globally and nasally reduced in glaucoma patients in both the superficial and the deep retinal plexus compared with healthy controls (Kromer et al., 2019). These results also align with Lommatzsch et al. (2018), who studied macular vessel density in glaucoma compared with healthy control eyes and found that both superior and deep retinal vascular plexus densities were lower in glaucomatous eyes than those in healthy eyes (Lommatzsch et al., 2018). Chao et al. (2019) found a similar decrease in the superficial capillary vessel density in OAG patients and normal tension glaucoma patients (NTG) compared with healthy controls (Chao et al., 2019). Chao et al. (2019) also reported a decrease in the deep capillary layers in NTG compared with controls. Notably, a significantly larger FAZ was found in NTG than in the ocular hypertension group (OHT) (Chao et al., 2019). Lu et al. (2020) compared perifoveal and parafoveal density in healthy controls, PPG patients and early perimetric OAG patients (Lu et al., 2020). Lu et al., (2020) found a significant decrease in the vessel density of the temporal quadrant of the parafoveal layer in PPG patients compared with healthy controls. Additionally, PPG patients also had a significantly decreased perifoveal vessel density compared with controls (Lu et al., 2020). In OAG patients, there was a significant decrease in the vessel density in both the parafoveal and perifoveal capillary layers compared with healthy controls, demonstrating a correlation between vessel density loss and increased severity of disease (Lu et al., 2020). Milani et al. (2021) compared healthy controls, ocular hypertension patients and OAG. Milani et al. (2021) found a significant decrease in whole-vessel density and parafoveal vessel density in the macular superficial capillary plexus in OAG compared with ocular hypertension patients and normal controls. This decrease in vessel density was measured both in the morning and in the evening demonstrating a consistent decrease in vessel density without diurnal variation (Milani et al., 2021).

In terms of the FAZ, Choi et al. (2017) found diagnostic value in the FAZ circularity index and perimeter. Specifically, eyes with glaucoma presented with decreased FAZ circularity index and increased FAZ perimeter compared with healthy controls (Choi et al., 2017). In addition to measuring macula vessel density, Shoji et al. (2017) compared the rate of vessel density loss among glaucoma, glaucoma suspect and healthy eyes. Of note, the authors found that the mean rate of change in macula whole en face vessel density was significantly faster in glaucoma eyes than that in glaucoma suspect eyes (0.85%/year, $p = 0.001$) and healthy eyes (0.29%/year, $p = 0.004$). This correlation remained consistent when comparing superior and inferior sectors of the macula (Shoji et al., 2017). Baek et al. (2019) specifically investigated the pattern and magnitude of diurnal variation in peripapillary and macular retinal vessel densities in subjects with OAG using OCTA. The authors found that in patients with OAG, the magnitude of diurnal changes in peripapillary RVD ($p = 0.013$) and macular RVD ($p = 0.042$) were significantly greater than those in the healthy controls (Baek et al., 2019). The magnitudes of diurnal variations in intraocular pressure and mean ocular perfusion pressure were also found to be greater in the OAG group than those in healthy controls (Baek et al., 2019). These results demonstrate that eyes with glaucoma present with not only reduced macular vessel density but also greater changes throughout the day compared with healthy controls, as measured by OCTA. Contrasting this, Verticchio Vercellin et al., (2020) recently did not find any statistically significant diurnal variation in ONH ocular blood flow measurements assessed by OCTA in OAG, OHT and healthy subjects.

#### Choroid layer OCTA vascular biomarkers

Significant differences in OCTA vascular biomarkers were also observed in the choroidal vasculature between glaucomatous eyes and healthy controls. Tepelus et al. (2019) found that patients with NTG had lower perfusion density of the

**Table 2.** Macula, fovea and perifoveal optical coherence tomography angiography (OCTA) vascular Biomarkers. OAG: open-angle glaucoma.

| Author (year) | Patients | OCTA scan | Results | p-value |
|---|---|---|---|---|
| Takusagawa et al. (2017) | 30 perimetric glaucoma<br>30 age-matched normal subjects | 6 × 6 mm macular | Superficial vascular complex and all plexus retinal vessel density were lower in the glaucoma group than those in the normal group | $p < 0.001$ for both |
| Kromer et al. (2019) | 30 OAG<br>21 healthy subjects | 5.0 × 3.5 mm Perifoveal | Macular flow density was globally reduced in glaucoma patients in the superficial plexus | $p = 0.0203$ |
| | | | Macular flow density was nasally reduced in the superficial plexus | $p = 0.0003$ |
| | | | Macular flow density was globally reduced in the deep retinal plexus | $p = 0.0113$ |
| | | | Macular flow density was nasally reduced in the deep retinal plexus | $p < 0.0001$ |
| Baek et al. (2019) | 20 OAG patients<br>19 healthy subjects | Macula 4.5 × 4.5 mm | Significantly greater diurnal changes in OAG in peripapillary retinal vessel density than healthy controls | $p = 0.013$ |
| | | | Significantly greater diurnal changes in OAG in macular RVD than healthy controls | $p = 0.042$ |
| Choi et al. (2017) | 52 patients with primary open angle glaucoma<br>52 healthy participants | Macula 3 × 3 mm | Macular vessel density was lower in OAG patients than normal controls in the superficial layer | $p = 0.013$ |
| | | | Macula vessel density was lower in OAG in the deep layer | $p < 0.001$ |
| | | | Macula vessel density was lower in OAG in the whole retina | $p = 0.002$ |
| | | | Increased foveal avascular zone perimeter and decreased foveal avascular zone circularity index in glaucoma patients compared with control | $p < 0.001$ |
| Shoji et al. (2017) | 38 healthy controls<br>30 glaucoma suspect<br>32 OAG | 3.0 × 3.0 mm Macula | Macula vessel density was greatest in healthy eyes, then glaucoma suspect and lowest in OAG | $p < 0.01$ |
| | | | Rate of change in macula vessel density was significantly faster in OAG (−2.23%/y) than that in glaucoma suspect eyes (0.87%/y) | $p = 0.001$ |
| | | | Rate of change in macula vessel density was significantly faster in OAG than that in healthy eyes (0.29%/y) | p=.004 |
| | | | Rate of vessel density loss in the superior and inferior regions of the macula was significantly faster in glaucoma patients than that in healthy controls or glaucoma suspect eyes | $p < 0.05$ |
| Chao et al. (2019) | 18 OAG<br>14 NTG<br>18 OHT<br>20 normal subjects | 3.0 × 3.0 mm macula | OAG and NTG had a significantly lower superficial vessel density than healthy controls | $p < 0.01$ |
| | | | NTG showed a significantly lower deep vessel density than healthy controls | $p < 0.01$ |
| | | | NTG group had a larger foveal avascular zone (FAZ) than the OHT group | $p < 0.01$ |
| | | | OAG group had lower flow area in the outer retina than the OHT group and control group | $p < 0.01$ |
| Lommatzsch et. al. (2018) | 85 eyes with glaucoma<br>50 healthy controls | 6 × 6 mm macula | Macular vessel density was lower in superficial retinal vascular plexus | $p < 0.0001$ |
| | | | Macular vessel density was lower in deep retinal vascular plexus | $p = 0.009$ |
| Lu et. al (2020) | 41 normal<br>44 pre-perimetric OAG (PPG)<br>42 early perimetric OAG (EG) | 6 × 6 mm macula<br>4.5 × 4.5 mm ONH<br>Radial peripapillary density measured using 750 μm wide elliptical annulus around disc | Parafoveal vessel density was lower in the temporal quadrant in PPG than that in normal controls | $p < 0.044$ |
| | | | Perifoveal vessel density was lower in the PPG group compared to normal controls | $p < 0.05$ |
| | | | Both parafoveal and perifoveal vessel density was lower in the EG group than that in normal controls | $p < 0.001$ |
| Milani et al. (2021) | 35 healthy controls<br>27 ocular hypertension (HTN)<br>24 OAG | 3 × 3 mm Macula | Mean whole vessel density in the macular superficial capillary plexus was highest in normal controls, followed by HTN, followed by OAG – during the morning (51.337 versus 50.781 versus 45.726, respectively) | $p < 0.0001$ |
| | | | Mean whole-vessel density in the macular superficial capillary plexus was highest in normal controls, followed by HTN, followed by OAG during the evening (51.504 versus 50.812 versus 46.069, respectively) | $p < 0.0001$ |
| | | | Mean parafoveal vessel density in the macular superficial capillary plexus was highest in normal controls, followed by HTN, followed by OAG during the morning (54.052 versus 53.472 versus 49.687, respectively) | $p = 0.0005$ |
| | | | Mean parafoveal vessel density in the macular superficial capillary plexus was highest in normal controls, followed by HTN, followed by OAG during the evening (54.037 versus 53.300 versus 50.154, respectively) | $p = 0.0022$ |

**Table 3.** Choroid layer optical coherence tomography angiography (OCTA) vascular markers. OAG: open-angle glaucoma; ONH: optic nerve head

| Author (year) | Subjects | OCTA scan | Results | p-value |
|---|---|---|---|---|
| Tepelus et al. (2019) | 26 low tension glaucoma (LTG) patients | 6 × 6 $mm^2$ macular layers | LTG group had lower perfusion density of the choriocapillaris than normal controls | $p < 0.001$ |
| | 22 age-matched healthy subjects | | LTG group showed reductions in vessel length density compared with controls for the superficial vascular plexus and optic nerve head + peripapillary area | $p = 0.03$ for both |
| Park et al. (2018) | 82 OAG with disc haemorrhage | 4.5 × 4.5 mm ONH | Choroid microvascular dropout was greater in patients with glaucoma and previous disc haemorrhage than glaucoma patients without previous disc haemorrhage | $p = 0.025$ |
| | 68 OAG without disc haemorrhage | | Within the disc haemorrhage group, progressive glaucoma patients (as defined by OCTA) had significantly greater choroid microvascular dropout than stable patients (77.3% versus 10.5%) | $p < 0.001$ |
| | | | Within the nondisc haemorrhage group, progressive glaucoma patients had significantly greater choroid microvascular dropout than stable patients (50% versus 23.1%) | $p < 0.001$ |

choriocapillaries than healthy controls. In addition, NTG eyes showed a decrease in vessel length density in other layers of the eye such as the superficial vascular plexus, optic nerve head and peripapillary areas compared with controls (Tepelus et al., 2019). These changes are consistent with earlier discussions of glaucomatous changes mentioned before. Changes in the choroid OCTA vascular biomarkers were also seen in severe OAG with disc haemorrhage compared with OAG without disc haemorrhage. Park et al. (2018) showed greater choroid microvascular dropout in OAG patients with previous disc haemorrhage than OAG glaucoma patients without previous disc haemorrhage. Park and colleagues also showed that within the disc haemorrhage group, progressive glaucoma patients (as defined by OCTA) had greater choroid microvascular dropout than glaucoma patients with stable glaucoma (77.3% versus 10.5%, respectively) (Park et al., 2018). Choroid microvascular dropout was also greater in progressive glaucoma patients in the nondisc haemorrhage group than that in stable glaucoma patients in the nondisc haemorrhage group (50% versus 23.1%) (Park et al., 2018). These studies provide evidence for greater OCTA vascular biomarker changes observed in the choroid layer of glaucomatous eyes than healthy controls, and differences in patients with progressive OAG versus stable OAG Table 3.

# Discussion

Optical coherence tomography angiography (OCTA) has emerged as a novel, noninvasive imaging modality combining clinical structural outcomes alongside vascular biomarkers in a single imaging modality. A wealth of pilot data has shown strong associations of OAG with lower OCTA assessed vascular biomarkers in the retina and ONH. However, data from large longitudinal studies of OCTA vascular biomarkers and glaucomatous progression remain missing, and the use of vascular outcomes in predicting OAG progression has not yet been realized. Examining the current literature reveals a strong uniformity of lower OCTA assessed vascular biomarkers in OAG patients, with supporting pilot data describing relationships to visual field loss and glaucomatous structural changes.

Specifically, both Jia and Lévêque showed a significant decrease in total capillary density and blood flow in the area of the optic nerve head in glaucomatous eyes compared with normal controls, indicating greater vascular abnormalities in eyes affected by OAG (Jia et al., 2012; Jia et al., 2014; Lévêque et al., 2016). Authors Liu, Chen, Triolo, Teplus and Akil showed significant decreases in vessel density and flow density in the peripapillary capillary layers of ONH in glaucomatous eyes and demonstrated greater areas of perfusion loss and low flow (Liu et al., 2015; Chen et al. 2016; Akil et al., 2017; Chen et al., 2017; Triolo et al., 2017; Tepelus et al., 2019; Chen et al., 2020; Lu et al., 2020). Similar significant decreases were identified in the circumpapillary vessel density among glaucomatous eyes compared with healthy controls, with the greatest decrease seen in severely glaucomatous eyes (Yarmohammadi et al., 2016a; Yarmohammadi et al., 2016b). Finally in patients with unilateral glaucoma, Kim and Mammo demonstrated greater vessel density changes in the affected eye than the fellow unaffected eye, showing that vascular biomarkers on OCTA are useful for tracking progression of glaucoma for each eye independently (Mammo et al., 2016; Kim et al., 2017).

In the macula, decreases in vessel density in glaucomatous eyes were seen in a number of capillary layers including the superficial vascular complex, deep retinal capillary layer and whole retina (Choi et al., 2017; Takusagawa et al., 2017; Chao et al., 2019; Milani et al., 2021). A decrease in flow density was also demonstrated by Kromer in both the superficial and deep capillary layers in the macula as a whole, as well as the parafoveal, perifoveal and nasal regions specifically (Kromer et al., 2019). There were also significant decreases in perifoveal and parafoveal vessel densities in OAG patients compared with healthy controls (Lu et al., 2020).

In the choroidal layer, lower perfusion density was seen in the choriocapillaris layer in NTG patients than controls (Tepelus et al., 2019). Choroid microvascular dropout was greater in OAG patients with previous disc haemorrhage than in patients without previous disc haemorrhage, and within groups, patients with progressive glaucoma had greater microvascular dropout than patients with stable glaucoma (Park et al., 2018).

Although OCTA has emerged as a powerful new imaging modality, it is important to acknowledge its

limitations. Firstly, OCTA specifically images the posterior retinal and choroidal microvasculature, which means that the complete ocular vascular system, including the retrobulbar vessels, cannot be analysed. Secondly, it is possible for the superficial layer of retinal vasculature to obscure the deeper vessels of the retina when imaged using OCTA, which may make interpreting the images more challenging. Furthermore, a high-quality OCTA image relies on the patient to remain still and avoid blinking. In addition, the presence of artefacts can make the OCTA scans more difficult to analyse (Koustenis et al., 2017). Lastly, Monteiro-Henriques et al. (2021) found that several patient characteristics including smoking status, hyper- or hypoxia conditions, and cardiovascular risk, among others, were related to ocular vascular changes. As a result, vascular biomarkers measured by OCTA may need to be adjusted to take into account such variables, but further research is needed in this area. Despite this, many OCTA devices offer a metric of scan quality for each image, which can aid clinicians in which scans they can reliably analyse and interpret. In terms of research evaluating the uses of OCTA for vascular biomarkers in glaucoma, more prospective longitudinal studies are needed as well as larger sample sizes.

Although vascular OCTA biomarkers provide valuable insights into glaucoma progression, standardization across different OCTA devices is an ongoing concern. In a study comparing the Optovue, Topcon and Zeiss OCTA devices, Lu et al. (2019) found significant differences in the superior capillary plexus and the deep capillary plexus in the macula (Lu et al., 2019). There was no significant difference in the foveal avascular zone (Lu et al., 2019). Another study compared 7 different OCTA devices in measuring the vessel density, fractal density and foveal avascular zone (VD, FD, FAZ) (Corvi et al., 2018). The comparison included Spectralis, Optovue, Angioplex, PlexElite, RS-3000 Advance, OCT-HS100 and Revo NX OCT-A devices (Corvi et al., 2018). There was a significant difference in the mean value produced by the 7 devices in both the superficial and the deep vascular plexus (Friedman test $p < 0.0001$) (Corvi et al., 2018). The authors of the study concluded that comparing the measurements of the VD, FD and FAZ among the 7 devices was not feasible (Corvi et al., 2018). This highlights the importance of the need for standardization among different devices and caution in making direct comparisons between devices (Corvi et al., 2018; Lu et al., 2019). In addition to inter-device variability, OCTA image data can differ based on software, protocol, processing and measurements generated (Spaide et al., 2018). There are currently a number of OCTA algorithms for analysing OCTA images including but not limited to optical angiography (OMAG), split-spectrum amplitude-decorrelation angiography (SSADA) and full-spectrum amplitude-decorrelation angiography (FSADA) (Rodríguez et al., 2018). These algorithms are often unique to the various OCTA devices that are currently on the market (Rodríguez et al., 2018). The differences in these measurement methods make comparing OCTA data between protocols and devices difficult, and standardization of OCTA vascular markers is necessary going forward (Spaide et al., 2018).

In conclusion, the ability for OCTA to quantify both clinical structural and blood flow changes to numerous vascular layers of the eye simultaneously makes it a promising tool for advancing OAG diagnosis and disease management. Vascular biomarkers from OCTA may be especially important in monitoring risk in persons with higher levels of vascular disease. Optical coherence tomography angiography is currently limited, however, by its variation in scan quality, influence of patient movement, potential for artefacts, lack of standardization in measurements and analysis, and differences among devices made by different manufactures who make direct comparison of OCTA data difficult. Future studies should be designed for understanding OCTA vascular biomarkers as predictors of disease progression by engaging in large and appropriately powered longitudinal studies of OCTA vascular biomarkers alongside traditional structural and functional measures of glaucoma progression.

# References


Akil H, Huang AS, Francis BA, Sadda SR & Chopra V (2017): Retinal vessel density from optical coherence tomography angiography to differentiate early glaucoma, pre-perimetric glaucoma and normal eyes. PLoS One **12**: e0170476.

Baek SU, Kim YK, Ha A et al. (2019): Diurnal change of retinal vessel density and mean ocular perfusion pressure in patients with open-angle glaucoma. PLoS One **14**: e0215684.

Chao SC, Yang SJ, Chen HC, Sun CC, Liu CH & Lee CY (2019): Early macular angiography among patients with glaucoma, ocular hypertension, and normal subjects. J Ophthalmol **2019**: 7419470.

Chen A, Liu L, Wang J et al. (2020): Measuring glaucomatous focal perfusion loss in the peripapillary retina using OCT angiography. Ophthalmology **127**: 484–491.

Chen CL, Zhang A, Bojikian KD et al. (2016): Peripapillary retinal nerve fiber layer vascular microcirculation in glaucoma using optical coherence tomography-based microangiography. Invest Ophthalmol Vis Sci **57**: 475–485.

Chen HS, Liu CH, Wu WC & Tseng HJ, Lee Y-S (2017): Optical coherence tomography angiography of the superficial microvasculature in the macular and peripapillary areas in glaucomatous and healthy eyes. Invest Ophthalmol Vis Sci **58**: 3637–3645.

Choi J, Kwon J, Shin JW, Lee J, Lee S & Kook MS (2017): Quantitative optical coherence tomography angiography of macular vascular structure and foveal avascular zone in glaucoma. PLoS One **12**: e0184948.

Corvi F, Pellegrini M, Erba S, Cozzi M, Staurenghi G & Giani A (2018): Reproducibility of vessel density, fractal dimension, and foveal avascular zone using 7 different optical coherence tomography angiography devices. Am J Ophthalmol **186**: 25–31.

de Carlo TE, Romano A, Waheed NK & Duker JS (2015): A review of optical coherence tomography angiography (OCTA). Int J Retina Vitreous **1**: 5.

Hou TY, Kuang TM, Ko YC, Chang YF, Liu CJ & Chen MJ (2020): Optic disc and macular vessel density measured by optical coherence tomography angiography in open-angle and angle-closure glaucoma. Sci Rep **10**: 5608.

Jesus DA, Barbosa Breda J, Van Keer K, Rocha Sousa A, Abegão Pinto L & Stalmans I (2019): Quantitative automated circumpapillary microvascular density measurements: a new angioOCT-based methodology. Eye (Lond) **33**: 320–326. https://doi.org/10.1038/s41433-018-0207-z.

Jia Y, Morrison JC, Tokayer J et al. (2012): Quantitative OCT angiography of optic nerve head blood flow. Biomed Opt Express. **3**: 3127–3137.

Jia Y, Wei E, Wang X et al. (2014): Optical coherence tomography angiography of optic disc perfusion in glaucoma. Ophthalmol **121**: 1322–1332.

Kim SB, Lee EJ, Han JC & Kee C (2017): Comparison of peripapillary vessel density between preperimetric and perimetric glaucoma evaluated by OCT-angiography. PLoS One **12**: e0184297.

Koustenis A Jr, Harris A, Gross J, Januleviciene I, Shah A & Siesky B (2017): Optical coherence tomography angiography: an overview of the technology and an assessment of applications for clinical research. Br J Ophthalmol **101**: 16–20.

Kromer R, Glusa P, Framme C, Pielen A & Junker B (2019): Optical coherence tomography angiography analysis of macular flow density in glaucoma. Acta Ophthalmol **97**: e199–e206.

Lévêque PM, Zéboulon P, Brasnu E, Baudouin C & Labbé A (2016): Optic disc vascularization in glaucoma: value of spectral-domain optical coherence tomography angiography. J Ophthalmol **2016**: 6956717.

Liu L, Jia Y, Takusagawa HL et al. (2015): Optical coherence tomography angiography of the peripapillary retina in glaucoma. JAMA Ophthalmol **133**: 1045–1052.

Lommatzsch C, Rothaus K, Koch JM, Heinz C & Grisanti S (2018): OCTA vessel density changes in the macular zone in glaucomatous eyes. Graefes Arch Clin Exp Ophthalmol **256**: 1499–1508.

Lommatzsch C, Rothaus K, Koch JM, Heinz C & Grisanti S (2019): Vessel density in glaucoma of different entities as measured with optical coherence tomography angiography. Clin Ophthalmol **13**: 2527–2534.

Lu P, Xiao H, Liang C, Xu Y, Ye D & Huang J (2020): Quantitative analysis of microvasculature in macular and peripapillary regions in early primary open-angle glaucoma. Curr Eye Res **45**: 629–635.

Lu Y, Wang JC, Zeng R et al. (2019): Quantitative comparison of microvascular metrics on three optical coherence tomography angiography devices in chorioretinal disease. Clin Ophthalmol **13**: 2063–2069.

Mammo Z, Heisler M, Balaratnasingam C et al. (2016): Quantitative optical coherence tomography angiography of radial peripapillary capillaries in glaucoma, glaucoma suspect, and normal eyes. Am J Ophthalmol **170**: 41–49.

Mansoori T, Sivaswamy J, Gamalapati JS & Balakrishna N (2017): Radial peripapillary capillary density measurement using optical coherence tomography angiography in early glaucoma. J Glaucoma **26**: 438–443.

Milani P, Urbini LE, Bulone E et al. (2021): The macular choriocapillaris flow in glaucoma and within-day fluctuations: an optical coherence tomography angiography study. Invest Ophthalmol Vis Sci **62**: 22.

Monteiro-Henriques I, Rocha-Sousa A & Barbosa-Breda J (2021): Optical coherence tomography angiography changes in cardiovascular systemic diseases and risk factors: A Review. Acta Ophthalmol. https://doi.org/10.1111/aos.14851.

Munk MR, Giannakaki-Zimmermann H, Berger L et al. (2017): OCT-angiography: A qualitative and quantitative comparison of 4 OCT-A devices. PLoS One **12**: e0177059.

Park HL, Kim JW & Park CK (2018): Choroidal microvasculature dropout is associated with progressive retinal nerve fiber layer thinning in glaucoma with disc hemorrhage. Ophthalmology **125**: 1003–1013.

Rodríguez FJ, Staurenghi G & Gale R (2018): The role of OCT-A in retinal disease management. Graefes Arch Clin Exp Ophthalmol **256**: 2019–2026.

Shoji T, Zangwill LM, Akagi T et al. (2017): Progressive macula vessel density loss in primary open-angle glaucoma: a longitudinal study. Am J Ophthalmol **182**: 107–117.

Spaide RF, Fujimoto JG, Waheed NK, Sadda SR & Staurenghi G (2018): Optical coherence tomography angiography. Prog Retin Eye Res **64**: 1–55.

Takusagawa HL, Liu L, Ma KN et al. (2017): Projection-resolved optical coherence tomography angiography of macular retinal circulation in glaucoma. Ophthalmology **124**: 1589–1599.

Tepelus TC, Song S, Borrelli E et al. (2019). Quantitative analysis of retinal and choroidal vascular parameters in patients with low tension glaucoma. J Glaucoma **28**: 557-562.

Triolo G, Rabiolo A, Shemonski ND et al. (2017): Optical coherence tomography angiography macular and peripapillary vessel perfusion density in healthy subjects, glaucoma suspects, and glaucoma patients. Invest Ophthalmol Vis Sci **58**: 5713–5722.

Verticchio Vercellin AC, Harris A, Tanga L et al. (2020): Optic nerve head diurnal vessel density variations in glaucoma and ocular hypertension measured by optical coherence tomography angiography. Graefes Arch Clin Exp Ophthalmol **258**: 1237–1251.

Wan KH & Leung CKS (2017): Optical coherence tomography angiography in glaucoma: a mini-review. F1000Res **6**: 1686.

Weinreb RN, Aung T & Medeiros FA (2014): The pathophysiology and treatment of glaucoma: a review. JAMA **311**: 1901–1911.

Weinreb RN & Harris A (2009): Ocular Blood Flow in Glaucoma: Consensus Series 6. Netherlands: Kugler Publications.

Yarmohammadi A, Zangwill LM, Diniz-Filho A et al. (2016a): Optical coherence tomography angiography vessel density in healthy, glaucoma suspect, and glaucoma eyes. Invest Ophthalmol Vis Sci **57**: 451–459.

Yarmohammadi A, Zangwill LM, Diniz-Filho A et al. (2016b): Relationship between optical coherence tomography angiography vessel density and severity of visual field loss in glaucoma. Ophthalmology **123**: 2498–2508.

Yarmohammadi A, Zangwill LM, Manalastas PIC et al. (2018): Peripapillary and macular vessel density in patients with primary open-angle glaucoma and unilateral visual field loss. Ophthalmology **125**: 578–587.

Received on March 17th, 2021.
Accepted on July 1st, 2021.

**Correspondence**
Alon Harris, MS, PhD, FARVO
Vice Chair of International Research and Academic Affairs
Director of the Ophthalmic Vascular Diagnostic and Research Program at Mount Sinai Hospital
Icahn School of Medicine at Mount Sinai
1468 Madison Avenue, Annenberg 22-86
New York, NY 10029
Tel.: 212-241-0250
C: 317-529-1033
Email: palonharris@gmail.com

†Indicates shared first authorship.

All authors made substantial contribution to the review. Each author participated in drafting or revising the manuscript and approved the submitted version for publication.

Professor Alon Harris would like to disclose that he received remuneration from Adom, Qlaris, Luseed and Cipla for serving as a consultant, and he serves on the board of Adom, Qlaris and Phileas Pharma. Professor Harris holds an ownership interest in AdOM, Luseed, Oxymap, Qlaris, Phileas Pharma and QuLent. All relationships listed before are pursuant to Icahn School of Medicine's policy on outside activities. Contribution of the author Francesco Oddone was supported by Fondazione Roma and by the Italian Ministry of Health. None of the other authors listed have any financial disclosures.

Alon Harris is supported by the NIH grant (R01EY030851) and NSF DMS (1853222/2021192). This work was supported in part by a Challenge Grant award from Research to Prevent Blindness, NY.