OCT-Angiography detects longitudinal microvascular changes in glaucoma: a systematic review

Short title: OCTA microvascular longitudinal changes in glaucoma: a review

Authors: Ana IM Miguel*, MD, PhD[1,2]; André B Silva*, MD[1,3]; Barbosa Breda J, MD, PhD[4,5,6]; Luís F Azevedo, MD, PhD[1]; Abdulkarim, Abdulrahman MD[7]; Hereth E[8], MD; Abegao-Pinto LB MD PhD[9,10]; Lachkar Y MD PhD[8]; Stalmans I MD PhD[6,11]

[1]Centre for Health Technology and Services Research (CINTESIS), Faculty of Medicine of Porto, Portugal

[2]Department of Ophthalmology, Hôpital Privé de la Baie, Avranches, France

[3]Department of Ophthalmology, Hospital São Teotónio, Viseu, Portugal

[4]Cardiovascular R&D Center, Faculty of Medicine of the University of Porto, Porto, Portugal

[5]Department of Ophthalmology, Centro Hospitalar e Universitário São João, Porto, Portugal

[6]KULeuven, Research Group Ophthalmology, Department of Neurosciences, Leuven, Belgium

[7]Mohammed bin Khalifa Cardiac Centre, Bahrain

[8]Department of Ophthalmology, Hôpital Saint-Joseph, Paris, France

[9]Visual Sciences Study Center, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal

[10]Department of Ophthalmology, Centro Hospitalar e Universitário Lisboa Norte, Lisbon, Portugal

[11]Department of Ophthalmology, University Hospitals UZ Leuven, Belgium

*Ana Miguel and André Silva have contributed equally and agree that both are 1st authors.

Corresponding Author: Ana IM Miguel, MD, PhD

Ophtalmologie, Polyclinique de la Baie, 3 avenue du Quesnoy, 50380 St Martin des Champs, France ; Phone: +33 787016187 ; Email: myworld_ana@hotmail.com

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Synopsis: A systematic review of studies of longitudinal changes in peripapillary and macular vessel density in glaucoma was performed. VD was smaller in glaucoma. Measures were suggested to decrease heterogeneity and increase the quality of studies.

Abstract

Background/Aims: Optical coherence tomography angiography (OCTA) allows the study of vessel density (VD). We intended to perform a systematic review of studies focusing on longitudinal changes in peripapillary and macular VD measurements in glaucoma.

Methods: A search was performed across MEDLINE, Scopus, ISI Web of Science, and Google Scholar, using the following query from inception until 20th September 2019: ((“optical coherence tomography angiography”[tiab]) OR (optical coherence tomography angiography[MeSH]) OR (“OCTA”[tiab]) OR (“OCT-A”[tiab]) OR (“angio-OCT”[tiab]) OR (“OCT- angiography”[tiab]) OR (“OCT-angio”[tiab]) OR (“OCT-angiographie“[tiab])) AND (glaucom*[tiab] OR glaucoma“[MeSH]). Prospective studies that quantitatively assessed the longitudinal changes in VD in glaucoma with at least three months of follow-up were included.

Results: Ten out of 4516 studies were included. The rate of VD change in glaucoma varied from 0.036/year to 1.08/year and 1.3% to 3.2% per year, with significantly different rates between glaucoma and healthy controls. Five studies assessed VD change after glaucoma surgery, obtaining variable results, ranging from a temporary VD decrease to increase after three months. Meta-analysis was not possible due to a wide variation in methods, measurements, and region of VD.

Conclusion: OCTA is non-invasive technology, which shows promise in glaucoma. Measures should be taken to increase the quality and standardise the methodology of VD measures in OCTA longitudinal studies, for future meta-analyses.

Keywords: ophthalmology; systematic review; glaucoma; prognosis; optical coherence tomography; optical coherence tomography angiography; OCTA; Angio-OCT; vessel density

Introduction

Glaucoma is a leading cause of irreversible blindness worldwide.[1,2] Optical coherence tomography angiography (OCTA) is a non-invasive imaging technology that creates high-resolution images of vascular structures across the retina and optic nerve without intravenous contrast.[3–5] OCTA has shown diminished vessel density (VD) in the peripapillary and macular areas in glaucoma compared to healthy controls.[6–8] Moreover, this technology has added values to OCT (optical coherence tomography). First, OCT provides limited information in myopic eyes since myopic tilted discs make acquisition and interpretation difficult.[9] OCTA has shown a lower VD in myopic patients with glaucoma, aiding in the diagnosis.[10] Second, the diagnostic capacity of OCT is limited in advanced glaucoma, where the retinal nerve fiber layer (RNFL) has become very thin (the so-called "floor effect").[4,11] Moreover, at this stage, visual field (VF) examinations are usually harder to perform and thus less reliable.[12,13] OCTA studies have shown that VD continues to decrease in advanced glaucoma, detecting progression even in the absence of measurable RNFL change.[14,15] Furthermore, OCTA imaging is less patient-dependent than VF examination and can therefore be more reproducible.[16] Third, OCTA may provide information on the vascular pathophysiology of glaucoma.[17]

Previous studies, including a meta-analysis[18], have shown that OCTA can be useful for glaucoma diagnosis.[19] More recently, studies have evaluated the ability of OCTA to detect and measure glaucoma progression.[20,21] Nevertheless, to our knowledge, a systematic review and meta-analysis are yet to be published.

This study's primary aim is to perform a systematic review of longitudinal VD changes detected by OCTA in patients with glaucoma and a meta-analysis. Secondary aims are the identification of heterogeneity moderators, such as the different methodologies used for VD quantification across different scans, devices, and glaucoma subtypes.

Methods

Our systematic review followed the guidelines of the Cochrane Collaboration[22], STROBE[23,] and MOOSE[24] checklists.

Terminology

VD is the percentage of area occupied by blood vessels, represented by lighter shades of grey. VD is measured quantitatively or qualitatively depending on the device used, which illustrates the need for standardised quantification methods[25]. The parafoveal VD is the VD between two circles centred in the fovea with diameters of 1mm and 3mm, and the perifoveal VD is within diameters of 3mm and 5mm. The peripapillary VD is the VD within a 750-µm-wide annulus extending from the optic disc boundary. Inside-disc VD is the VD within the optic disc boundary. The whole-image VD is the VD detected in the entire scan, which can be centred on the optic disc (4.5 x 4.5mm), the macula (6x6 mm), or the fovea (3x3 mm).

Search strategy

A comprehensive search was performed using four electronic databases from inception to September 20th 2019 - MEDLINE, Scopus, ISI Web of Science, and Google Scholar - using the query (MEDLINE): ((“optical coherence tomography angiography”[tiab]) OR (optical coherence tomography angiography[MeSH]) OR (“OCTA”[tiab]) OR (“OCT-A”[tiab]) OR (“angio-OCT”[tiab]) OR (“OCT- angiography”[tiab]) OR (“OCT-angio”[tiab]) OR (“OCT-angiographie“[tiab])) AND (glaucom*[tiab] OR glaucoma“[MeSH]). The query was adapted to each database (supplementary table1). Furthermore, through grey literature, unpublished data, and a hand search of references of the included studies and reviews, additional studies were identified. The review protocol was registered[26] on PROSPERO (record number CRD42020153576).

Eligibility criteria

Included studies fulfilled all the inclusion criteria listed below:

1. Primary aim of evaluating prospective glaucomatous changes using OCTA.
2. Studies either with primary open-angle glaucoma (POAG), or comparing healthy control subjects to POAG, diagnosed according to standard clinical criteria (i.e. optic disc and nerve fiber layer characteristics) and studied with either OCT or visual field (VF), or both.
3. Prospective, longitudinal studies with at least three months of follow-up.
4. VD quantitatively specified in: (a) whole-image optic nerve head; (b) peripapillary; (c) parafoveal; (d) whole-image macula.

No restrictions or limits were applied during the search process.

Exclusion criteria were: (1) non-glaucomatous diseases; (2) qualitative analyses; (3) studies reporting only sectoral VD (e.g., temporal peripapillary); (4) articles that did not report original data; (5) non-human subjects; (6) studies that failed to exclude poor-quality OCTA images (using signal strength index (SSI) <40/100 (Optovue®, Topcon®) or quality index (QI) <6/10 (Zeiss®)) and fixation artefacts or opacities; and (6) experimental and optics studies.

Data extraction

Two reviewers (A.M. and A.B.), independently read each title and abstract to exclude irrelevant studies and then independently reviewed each full-text to ascertain eligibility and to extract data. Disagreements were solved by consensus. A.M. contacted authors to acquire missing information and unpublished studies.

The primary outcome was the difference between mean VD, at baseline and at the end of follow-up in glaucomatous patients, and if available the difference between glaucoma and controls. The scan size, quality, region (whole-image optic nerve head, foveal, macular, peripapillary, or other), slab (choroid, optic nerve head, radial peripapillary capillary (RPC), vitreous), device, and method of VD assessment were reported. Other outcomes included the VF mean deviation, average OCT parameters and the coefficient of variation. The study design, participants' demographic data and follow-up time were recorded.

Quantitative analysis

Data analyses were performed using SPSS software v.17 (IBM, Armonk, NY, USA), and other analyses using Review Manager v.5.3. (Copenhagen)[27]. Between-group heterogeneity was tested using the I^2 test. Heterogeneity was expected, and subgroup analyses were planned, based on the type of glaucoma, minimal SSI/QI accepted, device, and being a surgical study.

Two independent reviewers performed data synthesis. As a primary outcome, either the difference in VD (%) before and at follow-up (3 months, 6 months and other time points) was assessed, or the slope (difference of VD) per year, if available. If sufficient data were available, a comparison between slopes in glaucoma *versus* healthy controls was recorded.

Risk of bias

For each study, two independent reviewers (AM and AB) performed a risk of bias assessment by applying the Cochrane's[22] tool and the STROBE[23]'s checklist. The criteria specific to low risk of bias in OCTA studies were:

1- Clearly stated "prospective" with specified follow-up;
2- Criteria for open-angle glaucoma with VF, OCT, and gonioscopy;
3- Arterial pressure measured;
4- Described quality of OCTA scans (reproducibility assessed; exclusion of poor-quality images; registered SSI/QI for each patient) and device;
5- Selection bias mitigated (eg. if case-control study, how were controls selected to guarantee that they did not have glaucoma);
6- Information bias mitigated (eg. if case-control study, did the controls perform the same exams than glaucoma patients);
7- Reported number of eyedrops at all follow-up points;
8- Specified outcomes (at baseline and follow-up): quantitative VD, OCT, VF;
9- Calculated sample size.

Disagreements were solved by consensus. Studies were reported as low risk (≥5 of the above criteria), medium (4 or 3 criteria), and high risk of bias (≤2 criteria).

Results

Study selection

From an initial selection of 4516 studies, ten[14,21,28–35] were included in the systematic review (Figure 1). A Kappa agreement of 0.81 was obtained for the eligibility of the full-texts (good agreement). The included studies are summarised in table 1. In supplementary table 2, the excluded studies are listed (from the 307 full-texts).

Figure 1

Table 1. ***Included studies.*** *The characteristics of the included studies are summarised.* Abbreviations: OCT, Optical Coherence Tomography; OCTA, Optical Coherence Tomography Angiography; VF, Visual Field; VD, Vessel Density; IOP, Intraocular pressure; RNFL, Retinal Nerve Fiber Layer; OAG, Open-Angle Glaucoma; POAG, Primary Open Angle Glaucoma, Losses to Follow-up (LFU).

Author, year	***Purpose of the study***	***Methods*** *- Study design* - Loss to follow-up (LFU) *- OCTA device*	***Participants*** *number of patients, eyes, mean age, % female, country*	***Outcomes*** ***-OCTA:*** *VD (VD_0 at 0 months; VD_6 at 6 months, VD_9 at 9 months, …), slope/year* ***- OCT:*** *RNFL (at 0, 6, 9,… months) and slope/year; GCC (at 0,6,9,… months)* ***- VF:*** *mean deviation(at 0, 6,…months) and slope/year;* ***Mean number of eyedrops***	***Conclusions and remarks***
Ch'ng 2019	To determine the effect of lowering IOP after glaucoma surgery on RNFL and VD (OCTA)	- Cohort - 1 year - 50% LFU or exclusions (80 eyes initially) - Optovue	- 40 eyes of 40 patients with OAG submitted to surgery; - age73.1±8.1 years - 55% female - Switzerland	- **OCTA**: **Foveal VD_0**: 25.6% (CI95%: 23.2,27.9); VD_6: 31.8% (CI95% 29.2,34.4); VD_{12}: 27.6% (CI95%: 24.8,30.4) (p<0.001). Slope : 1.07/year. « Superficial retina » slab. - **OCTA**: **Peripapillary VD_0**: 39.4% (CI95%38.5,40.3); $VD_{6months}$: 37.8% (CI95% 36.7,39.0); $VD_{12months}$: 38.2% (CI95%37.1,39.4) (p=0.09). Slab: not specified. - **$RNFL_0$**: 72.4 (71.0,73.7) µm, $RNFL_{12months}$ 71.3 (69.5,73.0) (p=0.03). - **VF** non mentioned. 2.2±1.2 **eyedrops** before Vs 0.4± 0.8 at 1-year after surgery -Glaucoma ***surgery***: mean IOP reduction of 30.5±22.8% at 12 months	- "Peripapillary VD fluctuated" - Foveal VD showed "near-normal reperfusion after glaucoma surgery." - Foveal avascular zone might be useful to assess reperfusion. - Complete VD data, but LFU
Hollo 2018	To utilize OCTA (peripapillary capillary VD) for the detection of glaucomatous progression, and to compare it with OCT (RNFL) and VF	- Prospective case-control - 2 years - Optovue	- 9 normal eyes, 20 with HTO, 24 POAG -59.3±14.4years in control, 61.2±8.8 in POAG - % female: ? - Hungary	- Slope/year (progression): 0.036 in capillary VD (statistically significant). - "The rate of statistically significant capillary VD progression ranged from -1.3% to -3.2% / year." - **Peripapillary VD** at 6 months, 12 and 24 months were only specified for the 4 patients that progressed. Slab: radial peripapillary capillary. -**RNFL**: 89.62 ± 9.70 µm in controls, 74.41 ± 14.88 in glaucoma; p<0.0001 -There was progression in the same 4 eyes by OCTA and **VF**	- Peripapillary VD did not identify progression, but peripapillary capillary VD did (in 4 from 24 glaucoma eyes) - "Sixteen of the 53 eyes progressed significantly for RNFL (P<0.0001)"
In 2018	To evaluate microvascular changes at the peripapillary area (PvD) and optic disc in glaucomatous eyes after IOP lowering by trabeculectomy	- Prospective cohort - 3 months - LFU undisclosed - Optovue	- 25 POAG patients, 25 eyes - age 61.12 ± 11.85 years - 40% female - Korea	- **OCTA**: *whole-image optic disc VD increased at 3 months (VD_0: 36.71±5.81; VD_3: 38.13 ±6.21 (p<0.05).* Calculated slope: 1.04 per 3 months. *- Peripapillary VD increased at 3 months postoperatively (43.02±6.83 preoperatively, and 45.11 ± 6.89 at 3-month, P <0.001).* Slab: radial peripapillary capillary. - **OCT, VF, Eyedrops**: not reported	- PvD decreased slightly at 1-week postoperatively, and after that, increased gradually, reaching a significant level at 3 months postoperatively *- Paired t-test was used (but did not report a test for normality)*

Kim 2018	To determine VD changes in the optic nerve head and peripapillary after trabeculectomy, and to correlate them with the lamina cribrosa (LC) curvature.	- Prospective cohort - 3 months - Topcon	- 56 POAG patients, 56 eyes - 55.6 ± 15.9 years - 26.8% (15) female - Korea	- **OCTA**: ***VD*** had increased significantly in the ***lamina cribrosa*** at 3 months postoperatively (from 10.21% ±4.72 to 11.88% ±6.04, p=0.006). - ***Peripapillary VD (lamina cribrosa slab)*** $_{baseline}$: 28.6±7.4; $VD_{3months}$: 28.2±7.7, p=0.558; - ***Peripapillary VD (choroid)*** $_{baseline}$: 75.4±10.4, $VD_{3months}$: 75.7± 10.5, p=0.637 -**VF**s were performed, but its results were included in a logistics model - No significant alterations in peripapillary VD, nor pre-laminary VD.	- A significant increase in lamina cribrosa VD was observed after trabeculectomy (which was more strongly associated with the reduction in the LC curvature than with IOP reduction).
Kim 2019	To evaluate the longitudinal change in the parapapillary choroidal dropout (MvD) in POAG, and its association with RNFL thinning.	- Prospective case series - 2.5±0.2 years - Topcon	- 68 patients with POAG and MvD, from a cohort - 54.5% (37) women - 54.3±13.1years - Korea	-OCTA: VD was not specified, but the area of MvD was: at baseline 0.507 mm^2; final follow-up: 0.665±0.496 mm^2 for the group with enlarged MvD and 0.297±0.189 for stable MvD. Slab/layer: choroidal. - OCT: *circumpapillary* RNFL and slope/year were reported - VF: specified at baseline but not for other time points (logistics model) - Eyedrops: not specified. Surgery was excluded	- "Faster RNFL thinning was associated with larger β-zone, disc haemorrhage, and a larger increase in MvD area".
Lommatzsch 2019	To investigate potential changes of vessel density (VD) at the optic nerve head and the macula 6 months after trabeculectomy	- Prospective - follow up period 6 months - Germany - Optovue	-19 eyes from 19 OAG patients submitted to trabeculectomy - 66.0±3.65 years - 58% (12) female - Germany	- **OCTA: Peripapillary VD** *not shown (an email was sent, without an answer). Figures suggest that authors also studied whole-image optic nerve VD, inside-disc VD, but the values are not specified.* ***Macular VD*** *and* ***whole-image optic disc VD*** *were assessed (but results are not specified).* Slab: radial peripapillary capillary. - **OCT**: $RNFL_{baseline}$: 74.0 ± 13.02 um; $RNFL_{6months}$: 73.94 ± 13.72 µm (p=0.88) - **VF**: no significant change (p=0.82) - **Surgery**: $IOP_{baseline}$ 21±1.97mmHg; $IOP_{6months}$: 10.26±2.81 mmHg (p<0.001)	- Excluded hypertension, diabetes, cardiovascular diseases and medication. - At 6 months: no significant change in neither ONH morphology (OCT) nor vessel density (OCTA)
Moghimi 2018	To investigate the relationship between macular (m-wiVD) and peripapillary vessel density and progressive retinal nerve fiber layer (RNFL) loss in patients with mild to moderate POAG	-Prospective - Mean of 27.3±3.36 months - 37 eyes LFU - Optovue	- 132 eyes of 83 POAG patients - age 68.7± 10.4 years - 86% (71) females - USA	- **OCTA: VD** was assessed (whole-image VD, peripapillary VD, macular VD) and modelled (linear mixed model), but not specified (email was sent to authors, without an answer). Slab: from the internal limiting membrane to the inner plexiform layer. - **OCT**: $RNFL_{baseline}$:79.5±14.8 µm, which declined with a mean slope of -1.07 mm/year (95%CI, -1.28 to -0.85). - "Each 1% lower macula VD and whole-image optic disc VD was associated with a 0.11-µm/year (P < 0.001) and 0.06-µm/year (P=0.031) faster rate of RNFL decline." - **VF**s were not performed	- Lower baseline macular and optic nerve head (ONH) VDs are associated with a faster rate of RNFL progression in mild to moderate glaucoma. - The "association between VD and RNFL loss rate was weak." - Some patients were submitted to surgery (not specified %)

Park 2019	To determine whether baseline parapapillary choroidal vessel density within the β-zone (VD) as measured by OCT-A was associated with future glaucoma progression.	- Prospective observational study - Mean follow-up of 2.6 years -14(11.4%) LFU - Topcon	- 108 patients - 59.2± 13.1 years - 69% (74) women - Korea	- **VF, OCT, OCTA** were measured, but since they are presented in a multivariable regression model, the crude values are not shown (we sent an email asking for the values at the end of follow-up). Slab: choroidal. Slope not reported. - $OCTA_{baseline}$: choroidal VD 47.0±6.54 % with progression and 52.54±10.40 without. The VD measured corresponds to the choroidal vessel density within the β-zone, which was manually calculated for each patient using software - $OCT_{baseline}$: 84.82±7.32 μm with VF progression and 85.21±8.95 μm without.	Lower parapapillary choroidal VD (odds ratio, 1.18; 95%CI: 1.09-1.28), disc haemorrhage and lower mean deviation were associated with glaucoma progression measured by VF, but not by OCT.
Shin 2017	To evaluate peripapillary microvascular changes and lamina cribrosa displacement (LCD) in patients with POAG after trabeculectomy.	- Prospective - 3 months FU - 14(31.1%)LFU - Optovue	- 31 eyes of 31 POAG patients - 56.1±12.1 years - 36.7%(11) female - Korea	- **OCTA**: ***peripapillary VD***$_{baseline}$: 44.9%±6.0%, $VD_{3months}$: 47.0%±7.2%, p=0.133. Slab: whole retinal layer. - At 3 months, intraocular pressure (**IOP**) and **LCD** decreased from 26.3±11.8 mmHg to 12.5±3.6 mmHg, and 501.1±130.2 μm to 455.8±112.7 μm (all p<0.001) - The ***microvascular improvement*** was defined as a reduction >30% of the area of vascular dropout (blue/black areas with <20% vessel density - **VF** did not change significantly	Microvascular improvement was observed in 19 eyes (61.3%) at 3 months after surgery. The reduction in LCD was significantly associated with microvascular improvement.
Shoji 2017	To characterize the rate of macula vessel density loss in primary open-angle glaucoma (POAG), glaucoma-suspect (GS), and healthy eyes.	- Prospective - Follow up: at least 1 year - 18 eyes (15%) LFU - Optovue	- 32 POAG, 30 GS, and 38 healthy eyes - 70.7±13.1 years in healthy, 71.8±9.7 POAG. - USA study - females: 52% in healthy, 41% POAG	**OCTA**: fovea VD_0: 52.3±3.1 % in healthy, 48.9± 4.5 in GS, 47.8±4.4 in POAG (p<0.001). Slab: macula superficial layer. **OCT**: GCC_0: 91.0±9.2 μm in healthy, 87.5±10.4 μm in GS, 74.0±11.7 μm in POAG (p<0.001) **VF** *median*±IQR: -0.6 (-2.2, 0.5) in normal, -0.8(-1.7, -0.1) in GS, -6.9(-11.3, -4.2) in POAG (p<0.01). *No VD, OCT nor VF values were reported at 6 nor 12 months, but the* rate of change was compared using a multivariate linear mixed-effects model.	The mean rate of change in macula whole-image VD was faster in glaucoma eyes (-2.23%/y) than in GS or healthy eyes (0.29%/y, P=0.004). There were no differences in the GCC change.

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The included studies had follow-up periods between 3 months[30,31,35] and 2.6 years.[21] There was a wide variation in the reported VD values, in the slab/retinal depth assessed, in the selection criteria, and the OCTA devices used. Five studies assessed VD before and after surgery[28,30,31,33,35]. The region of VD measurement varied from whole-image foveal[14,28,33,34], whole-image optic disc[30,34], peripapillary[28,29,31–33], peripapillary microvascular[28,29,35] (excluding large vessels), as well as personalised regions requiring manual selection for each patient, such as the lamina cribrosa VD[31,32], the VD within beta-atrophy area[21], the size of foveal avascular zone(FAZ)[28], and microvascular dropout area[31,32] (a focal sectoral capillary dropout with no visible microvascular network).

Risk of bias assessment

The risk of bias for the included studies is presented in supplementary table 3. Figure 2 presents the risk of bias summary. The outcomes measured varied widely (studies without all follow-up VD values[33]); none of the studies calculated sample size, and few studies had a low risk of bias.

Figure 2

Summary measures

1. Vessel Density (VD)

1.1. Whole-image optic nerve head (ONH)

Three studies reported the ONH VD[30,33,34]. A significant increase in VD was noted at 3-months post-trabeculectomy by one study[30], but not by another at 6-month[33]. Moghimi et al.[34] reported that each 1% reduction in ONH VD at baseline was associated with a 0.06 µm/year (P = 0.031) faster rate of RNFL decline.

1.2. Peripapillary

Ch'ng et al.[28] reported fluctuations in peripapillary VD after glaucoma surgery, ending with a non-significant change at 12 months. In et al.[30] and Shin et al.[35] reported a significant increase in peripapillary VD 3 months after glaucoma surgery, but not Kim et al.[31] Hollo et al.[29] used a cohort of 35 patients with two years of follow-up, and while no deterioration was detected using peripapillary VD, significant deterioration was after removing large vessels, in 4 patients. Deterioration was detected by VF in those four patients, and by OCT in 16 patients.

Park et al.[21] suggested that lower baseline VD (peripapillary choroidal beta-zone VD) could be associated with functional (VF), but not structural (OCT) progression (odds

ratio, 1.18; 95% CI, 1.09-1.28; P =0.01). Kim et al.[32] reported that the microvascular choroidal VD in the dropout area was not associated with the rate of RNFL thinning.

1.3. Macula

Four studies[14,28,33,34] measured macular VD changes. Two[28,33] evaluated VD changes post-surgery. In the first, superficial macular VD decreased slightly during the first month after surgery, then increased until 6 months, and then decreasing again at 12 months. Overall[28], there was a statistically significant increase of superficial macular VD at 12 months postoperatively, compared with baseline ($p< 0.05$). Parafoveal and perifoveal VD increased slightly but not significantly. Lommatzsch et al.[33] reported no significant VD change in the superficial or deep layers. Moghimi et al.[34] and Shoji et al.[14] documented significant changes in the rate of VD loss over time in glaucoma. The first[34] associated each 1% baseline reduction in macular whole-image VD with a 0.11 µm/year ($P<0.001$) faster rate of RNFL thickness decline; and with a faster rate of RNFL loss ($r^2 = 0.125$). The latter[14] demonstrated that the rate of macular VD loss in glaucoma eyes (-2.23%/year) was significantly faster than in glaucoma-suspect (+0.87%/year, P = .001) and healthy eyes (+0.29%/year, P = .004). There were no significant differences in the rate of change in the ganglion cell complex (GCC).

After glaucoma surgery[28], an increase in FAZ area at 1-month were detected, followed by a reduction from the 3rd month reverting to baseline at 1 year. No significant associations were found between VD changes and RNFL, IOP or SSI changes ($p>0.05$).

2. Retinal Nerve Fiber Layer (RNFL)

All but one study[35] reported the RNFL change during follow-up. Microvascular dropout area increase was associated with RNFL thinning.[32]

3. Studies evaluating glaucoma surgery

Five studies[28,30,31,33,35] evaluated the effects of glaucoma surgery in VD; the follow-up was of 3 months[30,31,35], 6 months[33] and 1 year[28]. All studies reported statistically significant IOP reduction after the procedures, but only two studies[28,33] reported the number of topical medications during the follow-up. Statistically significant microvascular improvement was observed in the peripapillary region in some studies[30,31], but not others[28,33,35]. One study[28] noted a significant increase in foveal VD at 3 and 6 months postoperatively with minimal changes at 1 month ($p < 0.01$), while

247 other[33] reported no significant differences. In et al.[30] reported a significant increase at
248 3-month postoperatively.

249 ***Sensitivity analysis***

250 Due to marked heterogeneity in methods and measurement of VD throughout
251 studies, a sensitivity analysis was not performed. Quantification was not possible.

252

253 **Discussion**

254 The number of published studies reporting the performance of OCTA in measuring
255 glaucoma progression is rising. Our group published in 2019 a meta-analysis[18] on the
256 diagnostic performance of OCTA in glaucoma. However, the challenge in glaucoma
257 management lies not only in diagnosis but also in progression detection, which requires
258 longitudinal OCTA studies. This systematic review presents a comprehensive search of
259 the literature, performed under strict criteria, providing an updated characterisation of
260 the methods and terminology applied in each study. We have assessed the role of OCTA
261 in measuring longitudinal and prospective VD changes and established a correlation with
262 progression of glaucomatous damage. An association was found between changes in
263 OCTA parameters and structural and functional decline across the majority of the
264 studies. VD decline correlated with baseline values[21,34], with the difference between
265 control and glaucoma[35], and with progression measured by OCT[33] and VFs[21]. Software-
266 assisted removal of large vessels[29] allowed the identification of a significant VD decline.
267 We found that the VD change in glaucoma ranged from 0.036 [29] to 1.08/year[28] and 1.3%
268 to 3.2% per year[30], with significantly different rates between glaucoma and healthy
269 controls.[14,30]

270 A study[21] reported a decrease in peripapillary choroidal VD within beta-zone in
271 eyes with glaucoma progression as measured by VF. A dropout in choroidal peripapillary
272 microvasculature was associated with RNFL thinning in POAG[32]. These two studies[21,32]
273 measured choroidal VD. Since two different vascular systems supply retina and choroid,
274 the results from these should be considered separately from the others. Nevertheless,
275 it seems that a decrease in VD is present in all studies in glaucoma.

276 We could not obtain data about the slope difference (or rate difference) in VD
277 between healthy controls and glaucoma patients.

Moghimi et al.[34] associated lower baseline macular and ONH VD with a faster rate of RNFL progression. However, they studied the relationship between baseline VD and the longitudinal RNFL changes, and not VD longitudinal changes directly. Shoji et al.[14] reported that POAG eyes had a significantly faster loss of macular VD than glaucoma-suspect or healthy control eyes, but the change in GCC thickness was not significant.

There was a significant increase in microvascular VD after glaucoma surgery[28,30,31,35], correlated with higher preoperative IOP, more significant IOP reduction and reduction of the lamina cribrosa depth. Ch'ng et al.[28] concluded that peripapillary VD was IOP-independent within the studied range of surgically controlled-IOP, while macular VD revealed a delayed response followed by near-normal reperfusion after glaucoma surgery. Lommatzsch et al.[33] did not find significant differences. Overall, these findings suggest that OCTA may be useful to evaluate the vascular recovery after glaucoma surgery. Further studies are needed to explore the association between VD and auto-regulatory mechanisms that are IOP-dependent.

A meta-analysis could not be performed since there was a wide variation in methodologies, measurements, slabs, regions, devices, and time points of measurement. We would like to encourage standardisation of measurements, quantification and analysis to produce better quality and more homogeneous studies in OCTA and glaucoma. We suggest an evaluation of VD systematically in the following regions (whole-image optic nerve head, peripapillary, foveal and macular); as specified in supplementary table 4 (which contains other suggestions). All VD measures should be specified at each time point. Very few studies reported all outcomes correctly and systematically, except for Ch'ng et al.[28] Some authors reported original VD assessment methods/regions, but not easily reproducible: VD of the lamina cribrosa[31], VD within the microvascular area[32], and VD within beta-region[21]. There is a multitude of devices, regions, and slabs to be assessed, but we need to understand the differences by performing comparative studies. To do so, we need to standardise the methods and improve the quality of studies, to allow meta-analyses.

Our study's strengths comprise a comprehensive search with strict criteria for glaucoma and detailed methodological review for each study, which highlighted the lack of standardised measurements. We propose a method for reporting VD in future studies.

This study suffers from some limitations. A meta-analysis was not performed as the studies presented significant heterogeneity in methods, measurements and outcomes, highlighting a lack of standardised measurements. The majority of the studies included VD parameters in a multivariable model analysis, which restricts generalisation of the results. Different regions were measured, therefore not comparable. Different slabs were used, as well as different size scans. Also, only some studies reported VD at the end of the follow-up[28, 30,31,34]. The studies included only POAG, which, despite being the most common type of glaucoma, limits the external validity of our review to other forms of glaucoma. No study calculated the sample size. The follow-up periods across studies were limited, which compromises the identification of confounders and detection of glaucoma progression.

Some limitations are related to OCTA technology: it is novel; therefore, few studies have evaluated glaucoma progression. Another limitation refers to scan quality; it is crucial to select only good quality scans with high SSI/QI. The inter-visit reproducibility was not frequently assessed. Arterial pressure, oral anti-hypertensive and topical hypotensive medications were not reported in most studies. They should be systematically assessed, because glaucomatous patients have a higher incidence of high arterial pressure[36], which has been shown to decrease not only the retinal capillary density[37] but also the thickness of the ganglion cell complex[38], constituting a confounder in OCTA studies. Arterial pressure[36–38] and IOP control[36,39,40] may help modulate ocular perfusion pressure. Considering that OCTA measures VD and microvascular circulation, it depends on arterial pressure and autoregulation. Moreover, the systemic hypotensive medication can also theoretically impact on the results.

In conclusion, OCTA has the potential to monitor microvascular changes in glaucoma, either related to glaucoma progression or surgical IOP lowering. However, the heterogeneity of study designs, methodologies, parameters, and reporting does not allow robust conclusions to be made around its validity for glaucoma follow-up in routine clinical practice. Automated quantification software and standardisation of methods are needed in future research.

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Legends of figures

Figure 1. Flowchart of search strategy. Flowchart according to Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE) guidelines[24].

Figure 2. Risk of bias summary. The risk of bias is presented for each study, according to Cochrane's guidelines[22] adapted to our study.