Type of the Paper (Systemic Review)

Optical Coherence Tomography Angiography: A Systematic Review and Meta-Analysis in Primary Glaucoma

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Received:	11 May, 2024	Reviewed:	19 June, 2024
Accepted:	20 July, 2024	Published online:	2 November, 2024

Abstract:

The diagnostic performance, benefits, and drawbacks of optical coherence tomography angiography (OCTA) compared to existing imaging modalities are still unknown. Using OCTA, we conducted meta-analysis research on vascular density (VD) in glaucoma patients. We examined the literature from January 2006 to March 2023 and also searched Web of Science, PubMed, Scopus, Google Scholar, ISI Conference Proceedings, and Prospective studies comparing the VD in open and closed-angle glaucoma using OCTA. The examination of meta-data contained 18 investigations out of 3045 evaluated publications. In 475 healthy eyes and 888 glaucomatous eyes, we found a statistically noteworthy decrease in the average peripheral visual defect (MPVD) in patients with glaucoma (57.53%, 95% CI: 52.60 to 62.46, p <0.001). When contrasted to controls (65.47%, 95% Confidence Interval 59.82-71.11); standardized (95% CI: –1.62 to –1.20, p <0.001), the mean difference [SMD], –1.41). Likewise found that the mean-parafoveal VD (SMD, –3.92, 95% CI: –4.73 to –3.12, p <0.001), mean inside-disc VD (SMD, − 9.51, 95% CI: –12.66 to –6.36, p <0.05), and mean entire optic nerve image VD (SMD, –9.63, 95% CI: –10.22 to –9.03, p <0.001). A considerable variation within the MPVD was seen between glaucoma types and OCTA devices based on subgroup studies (open-angle vs. closed-angle glaucoma). In conclusion, OCTA is a reliable diagnostic tool for glaucomatous eyes, but further research is needed to understand the vascular changes linked to open and closed-angle glaucoma.

Keywords: Optical coherence Tomographic Imaging Angiography; Primary Open Angle Glaucoma; Angle Closure Glaucoma.

1. Introduction

Retinal ganglion cell degeneration, distinctive alterations to the normal visual field (VF), the optic nerve head, and the thinning retinal nerve fiber layer (RNFL) deficits are the hallmarks of the progressive optic neuropathy known as glaucoma. The two types of primary angle-closure glaucoma (PACG) and primary open-angle glaucoma

(POAG) are two subtypes of primary glaucoma that are distinguished by the anatomical nature of the angle of the anterior chamber [1]. In Asia, PACG is the predominant cause of blindness, accounting for 25% of instances with primary Global glaucoma prevalence [2]. While more people have POAG than PACG. in most populations, PACG is more frequently connected to severe and bilateral vision loss [2-5].

The pathophysiology of PACG is still unknown. Angle closure-induced increased IOP is the primary cause of PACG [6]. Poor ONH perfusion and vascular abnormalities are other non-IOP risk factors that lead to POAG injury [7-9]. PACG may also be caused by vascular causes. By increasing IOP, PACG can alter ocular perfusion and induce ischemic damage to intraocular tissues [10, 11]. Reduced ocular blood flow in PACG may impair microvascular in the peripapillary and macular perfusion tissues.

OCTA stands for optical coherence tomography angiography, a relatively new kind of imaging, that uses motion contrast produced by red blood cells in motion to rapidly and noninvasively assess the macular, peripapillary, and ONH regions [12-15]. Density of arteries (VD) measures in the macula, peripapillary retina, and optic nerve allow us to provide both quantitative and qualitative data about using the microvasculature's amazing repeatability and reproducibility thanks to the most recent advancements in OCTA. Through the use of superficial vascular network OCTA pictures, we may calculate the area of foveal avascularity (FAZ). Vascular variables engage in play a major part in the development of glaucoma, as evidenced by recent OCTA experiments that indicate reduced macular and peripapillary visual defects in glaucomatous eyes to correspond Using the visual field (VF) impairment. [16-19]. Prior studies conducted by OCTA concentrated on cardiovascular elements in POAG optic neuropathy due to glaucoma [14-19]. However; distinct pathways have been linked to the pathophysiology of PACG vs POAG [10, 11].

Our goal in this work was to perform A comprehensive review of macular and peripapillary VD in glaucoma patients in comparison to wholesome safeguards, as well as between glaucoma's two types, open angle and closed angle).

2. Methods

We followed the Cochrane Collaboration's criteria while performing a meta-analysis [20]. From January 1, 2006, to March 9, 2023, we used the following search

query to access MEDLINE, Scopus, Web of Science, and Google Scholar. methodically and thoroughly: TOMAG (optical coherence tomography angiography) OR (optical coherence tomography angiography (MeSH) Alternatively, OR ("OCTA"[tiab]) OR ("OCT-A"[-tiab]) OR ("angio-OCT"[tiab]) OR ("OCT-angiography"[tiab]) OR ("OCT-angio"[tiab]) OR ("OCT-angiography"[tiab]) OR ("OCT-angiography"[tiab]) AND (glaucom*[tiab] For glaucoma, see [MeSH]). The procedure for the review wasn't recorded. In addition, we manually looked over the included reference papers and assessments as well as the unreleased data and the grey literature.

Eligibility requirements

Research that matched each of the subsequent inclusion requirements was incorporated:

- The main objective of assessing OCTA's diagnostic efficacy in glaucoma.
- Research that contrasts healthy control subjects who do not have glaucoma or any ophthalmological or systemic pathologies with glaucoma patients based on conventional clinical parameters. That included nerve and optic disk fiber layer traits, intraocular pressure; and complementary analysis (using visual field, VF, or OCT).
- Studies with a prospective design that uses a cross-sectional, cohort, or case-control methodology. Studies without a stated date of participant addition were disqualified (unless the sample group was part of a planned longitudinal research).
- At least one of the following three diagnostic studies— the optic nerve head in full view, the complete peripheral scan, and the parafoveal scan—has quantitative VD specifications. Our review's goal was not to examine prognostic studies or lengthy longitudinal data.

Exclusion criteria

That included:

- Research on non-glaucomatous diseases unless glaucoma and healthy controls were included.
- Qualitative analyses (many OCTA gadgets only supply high-quality pictures).
- Research focusing just on sectoral VD (e.g., only Unless they reported complete peripapillary VD, in temporal peripapillary).
- Studies conducted on non-human participants.
- Research that did not exclude low-quality index OCTA pictures, such as a fixation signal strength index (SSI) of less than 40, or less than 6 for Zeiss device artefacts, or the opacities of media.
- Experiment and optical research.

2.1. Information Extraction

The average VD-expressed proportion of glaucoma patients compared to control participants either the macular scan (with SD) or the optic nerve head scan, was the main diagnostic outcome. Furthermore, we documented the dimensions of the scan (e.g., Measurements: 3 mm by 3 mm), the kind of the OCTA scan (e.g., entire-image optic nerve), the Evaluation of VD technique (e.g., software-calculated or provided by the device), the VD definition as stated, the OCTA gadget utilized, the acceptable minimal SSI for a high-quality scan, and if the writers of the study clarified the microvascular abandonment. The VF's mean deviation and structural metrics obtained by OCT, the coefficient of variation, and the area under the curve (AUC) of the OCTA diagnostic ability were among the other outcomes recorded. In addition, we documented the plan of the study and duration of recheck, the total amount of participants, the number of glaucoma patients' eyes and their kind, the number of robust benchmarks and the healthy controls' eyes that were studied, the mean age, the percentage among participants who were female, the nation, and an overview of the research.

2.2. Quantitative analysis

Excel and SPSS V.17 were used for data analysis. Using the Copenhagen version of Review Manager V.5.3, we carried out subgroup analysis, heterogeneity analysis, random-effects meta-analyses, and quality evaluation graphs for standardized mean variation (SMD) [21]. Subgroup analysis was designed according to the equipment, minimal SSI allowed for OCTA scans and kind of glaucoma, and we tested for utilizing the in-between group heterogeneity I2 test. Diversity was anticipated. Should writers introduce "pre-perimetric glaucoma," we evaluated the requirements for glaucoma inclusion to determine if this particular subgroup was comprised.

3. Results

24 papers were ultimately included in the retrieval, which produced 3045 titles in total (**Figure 1**). Good agreement, or 0.79, was the Kappa agreement. The difference in SMD between controls and glaucoma in the peripapillary VD was the main result. The whole-image visual acuity, whole-image macular, and whole-image parafoveal visual outcomes were the secondary diagnostic outcomes. Eight studies showed the parafoveal VD, three showed a measure of peripapillary flow, two showed the entire picture macula

using three mm by three mm scans, one with scans of 6 mm × 6 mm, and two showed the peripapillary VD. Of the eight research that were part of the meta-analysis, nine presented the whole optic nerve VD. Five research were not contained in our meta-evaluation: two [22, 23] displayed just the VD median values and three [24, 25, 26] showed the capillary but not the entire vector domain. Conversely, Geyman et al. (2017) study included despite having also reported the total VD and having examined the capillary VD [27].

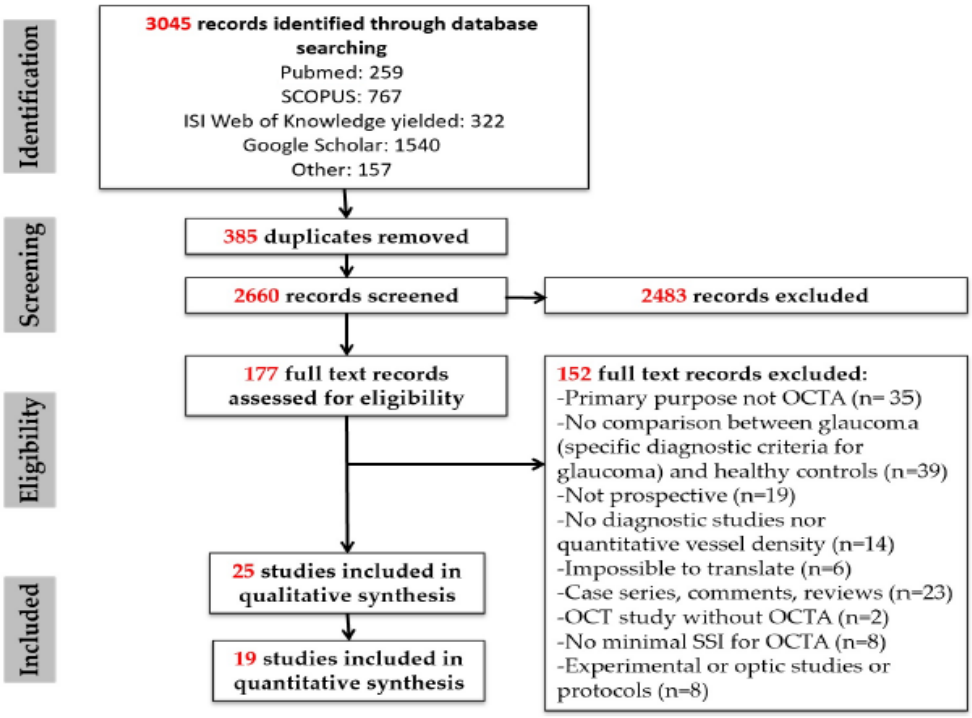

Figure 1: Flow diagram for the search approach. The search plan is depicted in the flow chart by the recommendations of the Systematic Reviews of Observational Studies and Meta-Analyses. SSI stands for signal strength index; OCT stands for Coherence tomography using optics; and Optical coherence tomography angiogram using OCTA.

Figure 2 shows the corresponding forest plot. average VD of the peripapillary in glaucoma 57.53% (95% CI: 52.60 to 62.46) of the patients and subtype SMD, –1.41, 95% CI: –1.62 to –1.20, p <0.05) in controls (65.47% 95% CI: 59.82 to 71.11). This represents 475 healthy eyes and 888 glaucomatous eyes overall. Significant heterogeneity was found (I2 =59%) cases. The radial section of the peripapillary capillary—the slab supplied by the device—was the one examined in each study. With a 4.5 scan size x 4.5 mm, the average whole-image VD centered in the head of the optic nerve had an I2 of 86% and

an SMD of –9.63 (95% CI: –10.22 to –9.03, *p* <0,05). Additionally, according to Lévêque et al., (2019) but with scans of just 3 mm by 3 mm; as a result, adding it to the forest plot was incorrect [28]. Two investigations reported on the VD inside the disc [28, 29] and had an SMD of -9.51 (95% CI: -12.66 to -6.36, *p* <0.05) without any statistical variability (I2 of 0%). In whole-image macular VD (scans of 6 mm by 6 mm), the mean value was only provided by a single research [30]. In contrast, the 3 mm x 3 scans Figure 3: One inquiry displays the glaucoma-based subgroup analysis of the peripapillary VD [30]. In contrast, the 3 mm x 3 scans Figure 3 displays the glaucoma subtype-based subgroup analysis of the peripapillary VD: a single inquiry [31] examined glaucoma with main angle closure, [32, 33] Nine investigations examined POAG, or primary open-angle glaucoma (I2 =0%), three evaluated other forms of glaucoma (mixed/grouped) (I2 =47%), and two examined normal-tension glaucoma (I2 =95%).

Two investigations utilized a Zeiss instrument (p <0.05, SMD, -1.13, 95% CI: -1.56 to -0.70), I2=0%), while 17 studies used SMD, -1.68, 95% CI: -2.03 to -1.34, p <0.05) for an Optovue device, I2=87%), according to the subgroup analysis of OCTA devices. The four low-risk-of-bias peripapillary VD studies had an I2 of 0%, eight studies with bias with a moderate risk had an I2 of 62%, and three studies with strong potential for prejudice had an I2 of 84%, according to the bias risk in subgroup analysis (**Figure 3**).

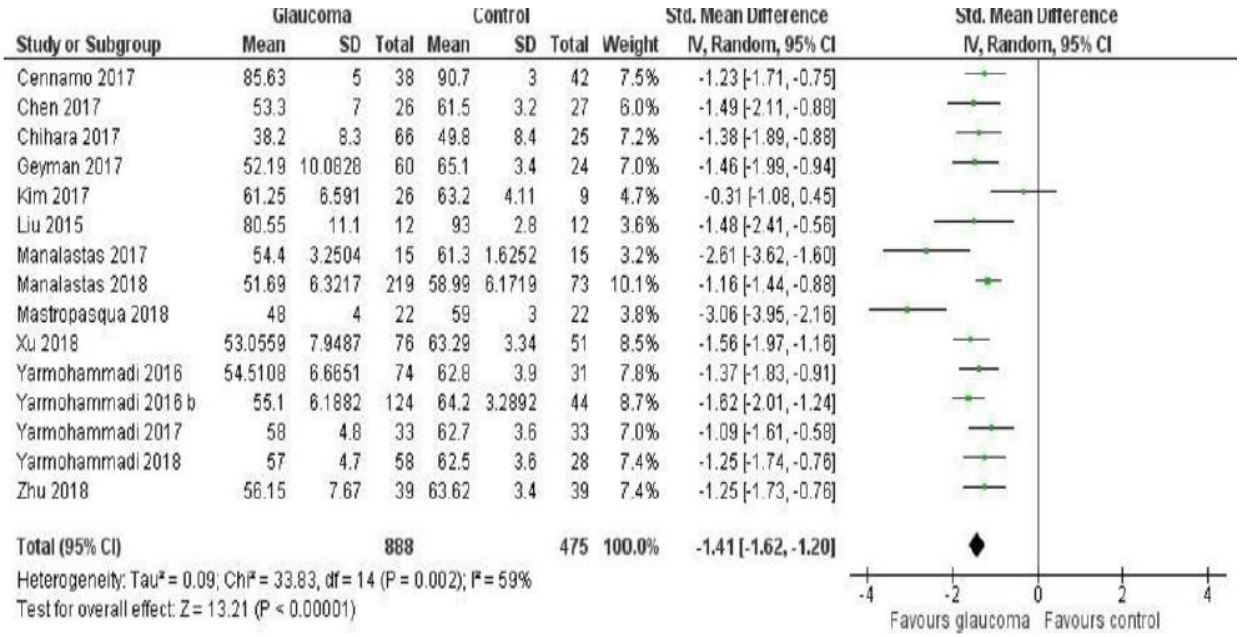

Figure 2: Peripapillary vessel density in a forest patch. Peripapillary vascular density meta-analysis, expressed as a percentage, mean, and standard deviation. IV: inverse variance technique

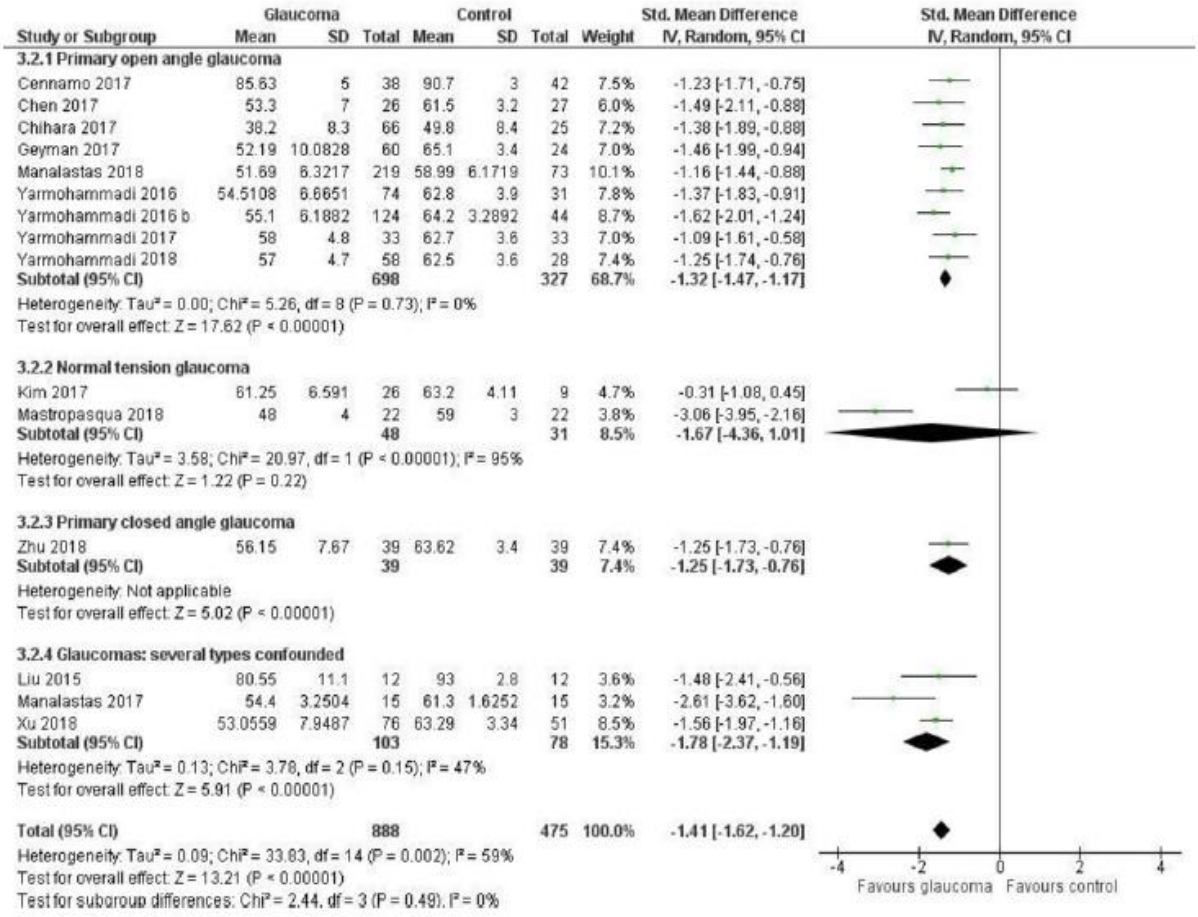

Figure 3: Subgroup analysis based on glaucoma type. Peripapillary vascular density subgroup analysis based on glaucoma subtype. Percentage is used for units. IV: the variance inverse technique.

In this review, we conducted two post-hoc subgroup analyses: the first was in between the nine trials that measured blood pressure, I2 =0%) and without six research, I2 =83%), and the second was between the overall VD peripapillary (19 studies, I2 =59%) capillary VD (four investigations), I2 =93%). Except for the subgroup VD based on the apparatus (I2 =74%), no heterogeneity (I2 =0%) was found by the test for subgroup differences in any subcategory evaluations.

4. Discussion

There has been an exponential rise in the quantity of published research detailing OCTA's diagnostic efficacy in glaucoma. Reviews from the past have discussed the algorithms and repeatability of OCTA [3, 5]. But We are pioneers in offering a comprehensive and current characterization of research on OCTA in glaucoma; identifying variations in the approaches and vocabularies employed in every research; assessing the potential for prejudice in the included research; and offering several measurements of the VD's meta-analysis for differentiating between healthy and glaucomatous eyes. We combined the whole-image, parafoveal, inside-disc, and mean peripapillary visual acuity (VD) and entire picture VD in glaucoma. We show that OCTA may help in the diagnosis of glaucoma, showing that in all investigated locations, the VD has much-reduced levels of glaucoma patients than in wholesome guidelines. When reported, the AUC of OCTA's diagnostic ability was good (0.983) [30]; Unfortunately, there was just one study, therefore We couldn't carry out a meta-analysis. [22] published 95% confidence intervals. When comparing the AUC of OCTA with OCT, several researchers came to various conclusions; four studies [25, 29, 34, 35] revealed a higher than average OCTA AUC, five had lower [22, 27, 36, 37], and two said there was no change [22, 38]. There was no association found in one investigation between OCT and OCTA [26]. Four research suggest that OCTA may offer structural and functional information on glaucoma [13, 29, 37, 39], VF and VD had a stronger association than VF and OCT; one study found the same results [30]; Another failed to find any meaningful association [40]. The reported values of the OCTA coefficient of variation ranged from 2.3% to 4.1% [30, 34] indicating superior repeatability than that of virtual figures [36]. As a result, OCTA may offer a more impartial, quicker, and less erratic test than VFs, the industry normative for gauging the course of glaucoma.

The two studies that most increased the heterogeneity of the meta-analysis were those by Mastrophasqua et al. (2018) and Kim et al. (2017) [32, 33] Mastrophasqua et al. (2018) revealed the largest SMD and glaucoma's lowest mean VD among all the studies, which may account for the observed variability since they examined normal-tension glaucoma, which is thought to have a more pronounced vascular alteration [2] The study focused on acute ischemic optic neuropathy [32]. It can explain a methodological inconsistency. Kim et al. (2017) examined eyes with standard-tension

glaucoma, however unexpectedly found the VD ranking third [33].

Due to intrauser variability and bias, the authors evaluated the eyes of two glaucoma patients, one with VF changes and another who had preperimetric glaucoma. In contrast to the results of Kim et al. (2017) study, wherein compared to healthy individuals, other studies revealed that preperimetric glaucoma showed reduced peripapillary VD [29, 40]. We constructed a different forest plot, omitting the study's preperimetric ocular glaucoma by Kim et al. (2017) I2 =49% indicates reduced heterogeneity [33]. Another drawback of the research by Kim et al. (2017) is that the patients and controls' ages differed significantly [33]. Subgroup analyses evaluated the heterogeneity between study categories in this work, and studies involving individuals with POAG, studies with minimal risk of bias, and blood pressure studies showed no statistical heterogeneity between studies. About the glaucoma subtype, Mastropasqua et al., 2015 found high heterogeneity (I2 =93%) in normal-tension glaucoma, while examining peripapillary VD in POAG with an I2 of 0%. [32] and Kim et al. (2017) [33] for the previously stated explanations. An I2 of 0% was also obtained as a breakdown by a subgroup of low study bias danger, supporting the need for a rigorous approach. The subset of research that measured blood pressure could be similarly justified since they likely used a stricter approach, which accounts for their I2 of 0% value. Concerning the subgroup analysis using the OCTA device, the I2 for two Zeiss experiments was 0%, whereas the I2 for seventeen Optovue studies was 87%. The Zeiss and Optovue groups showed heterogeneity (I2 =74%), indicating that various instruments evaluate peripapillary VD in different ways (the Zeiss trials indicated lower mean VD). The observed variation may have implications for the diagnosis of glaucoma. Therefore, we advise developing separate analysis and quantification software for VD and disseminating the previously created, customized applications to contrast the VD found by various devices [24, 27]. Moreover, to determine the variations in measurements in each device, subsequent research should employ various devices on the same patients.

Few studies either disclosed the average SSI or employed techniques to lower the variability in VD linked to SSI [22, 26]. There is increasing evidence that the VD and the SSI are correlated and increase bias (even with modern software and optics for reflectance adjustment) [26, 30, 37]. Chihara et al. (2017) used a straightforward but successful tactic: dividing the VD by the SSI

[41]. Therefore, we urge all upcoming research to provide the mean SSI (with SD) for patients and controls, along with the VD and VD/SSI as outcomes.

The rigorous criteria for defining glaucoma, the broad rise in the systematization of OCTA in glaucoma provides thorough methodological information for every study that's included, and the execution of studies of subgroups and meta-analyses, which allowed the writers to provide an overview of values-free of statistical variations, are the main this systematic review's strong points.

Two trials showed mm, with an I2 of 11% and an SMD of −4.81 (95% CI: −5.97 to −3.66, p <0.0001) [36, 42]. With an SMD of –3.92 (95% CI: –4.73 to –3.12, p <0.0001) and an I2 of 53%, the pooled mean parafoveal VD was 48.05% (95% CI: 46.73 to 49.37) in glaucoma and 52.09% (95% CI: 50.17 to 54.01) in controls. Three studies evaluated the peripapillary flow index, which showed an I2 of 74% and an SMD of –1.53 (95% CI: –2.29 to –0.78, p <0.05).

On the other hand, this comprehensive review is not without flaws. The first type of heterogeneity is shown in whole-image macular VD, whole-image optic nerve VD, parafoveal VD, and global peripapillary VD. Nonetheless, we anticipated this variability, and the subgroup analyses helped to partially resolve it. The second factor is the included studies' cross-sectional study design, which is particularly vulnerable to biases in information and selection. Lastly, publication prejudice may be indicated by a funnel plot for the peripapillary VD that is not perfectly symmetrical.

5. Conclusions

Because OCTA is quick and non-invasive, it may help identify vascular alterations associated with glaucoma and, as a result, identify the condition earlier. According to this comprehensive review, glaucoma patients have lower peripapillary visual loss when compared to healthy controls. We encourage further research using a prospective longitudinal strategy.

Funding: We did not get any particular grants from governmental, commercial, or non-profit funding entities.

Conflicts of Interest: All authors declare no conflict of interest.

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